Ring Chromosomes 13 and 14 presenting as intractable seizures- report of two cases with unusual features and review of literature

Divya Pachat[1], Karthik M[2], Vivi Srivastava[3], Maya Thomas[2] and Sumita Danda[1*]

[1]*Clinical Genetics Unit, Christian Medical College and Hospital (CMCH), Vellore, India*

[2]*Pediatric Neurology Unit, Christian Medical College and Hospital (CMCH), Vellore, India*

[3]*Cytogenetics Unit, Christian Medical College and Hospital (CMCH), Vellore, India*

Email: sdanda@cmcvellore.ac.in

Abstract

Ring chromosomes (RC) result from terminal deletion of chromosome arms, followed by fusion of the broken ends leading to the loss of genetic material. The phenotype is determined by the chromosome involved and the extent of deletion. Ring chromosome (RC) is a rare cytogenetic abnormality which should be considered in children with intractable seizures and developmental delay. Peripheral blood karyotype can easily identify such cases. We present two cases where chromosome analysis was performed; a girl presenting with intrauterine growth retardation, microcephaly, intellectual disability and early onset difficult to control seizures and a boy with uncontrolled seizures, dysmorphism and craniosynostosis. Chromosome analysis revealed RC13 in the girl and RC14 in the boy. Refractoriness of seizures in RC13 and craniosynostosis in RC14 that are reported here have so far not been described in literature. This report suggests that RC13, invariably leading to group 3 category of deletion 13q syndrome, may be more severe than previously indicated and the case with RC14 expands the phenotype of RC14. Uncontrolled seizures in a child with developmental delay with or without dsymorphism should warrant a chromosomal analysis.

Introduction

Ring chromosomes (RC) usually result from two terminal breaks in both chromosome arms, followed by fusion of the broken ends leading to the loss of genetic material.[1] The most important factor affecting the phenotype of patients with RC is chromosome type and the extent of the deletion of the genomic segments containing crucial genes for a normal development.[2] The large spectrum of clinical phenotypes of RC 13 and 14 is similar to that of large deletions involving the q arms of these acrocentric chromosomes and has been described under "ring 13/14 chromosome syndrome". Though uncommon, these are now considered as well-recognizable chromosomal abnormalities due to a pattern of common dysmorphic features and malformations. Techniques like array comparative genomic hybridization (array-CGH), fluorescence in situ hybridization (FISH) and MLPA (Multiplex Ligation-Dependent Probe Amplification) have allowed improved molecular genotype-phenotype correlations by means of accurate delineations of the deleted regions and precise molecular karyotyping.

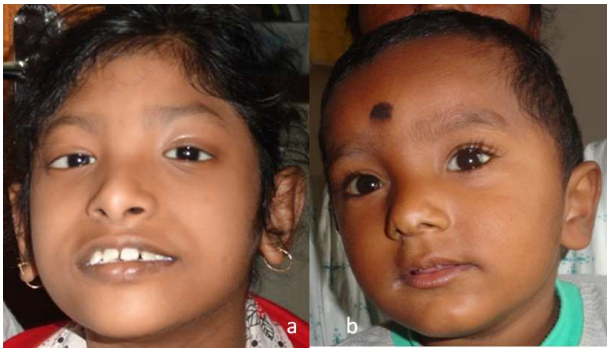
Described by Lejune *et al.* in 1968, RC 13 is relatively uncommon; with an estimated incidence of 1/58,000 live births.[3] Occurrence of RC 14 syndrome also is relatively rare with over 70 cases reported so far.[4] We present here two cases: one with unusual presentation of seizures in a girl with RC 13 and another with additional finding of craniosynostosis in a boy with ring chromosome 14, so far not described in literature.

Case reports:

- Case 1: A 10 year old girl presented with history of seizures and developmental delay from

early neonatal period. Oligohydramnios and intrauterine growth retardation were detected in the antenatal period. She was the first offspring of non-consanguineous healthy parents. She was born at term gestation with a birth weight of 2 kgs and cried around 10 minutes after delivery, following stimulation. She was on valproate therapy intermittently from day one of her life and had uncontrolled seizures. The parents had noticed significant global developmental delay since early infancy with behavioural issues such as aggressive behaviour, bruxism and abnormal laughter. Her younger brother was healthy. Her height, weight and head circumference were around 3SDs below the mean Indian standards. The dysmorphic profile of the patient is described in Figure 1a. and Table 1. Rest of the physical examination was normal. Her complete blood counts (CBC), metabolic work up, electroencephalogram (EEG) and magnetic resonance imaging (MRI) of brain were normal. Peripheral blood karyotype showed ring chromosome 13, 46,XX,r(13)(p13q34), in all 20 metaphases (Figure 2a). Fluorescence in situ hybridization (FISH) analysis of 200 interphase cells confirmed deletion of the D13S1825 locus on chromosome 13, band q34. Karyotype of the mother was normal. Father's karyotype showed an additional material on the short arm of chromosome 15, 45,XY,add(15)(p13) in all metaphases which was due to a balanced translocation involving chromosomes Y and 15, t(Y; 15)(q12; p11.2). Neither parent had ring chromosomes or any other abnormality involving chromosome 13.

- Case2: A 15 months old boy, first born of non-consanguineous healthy parents, presented with seizures since 1 month of life, requiring multiple antiepileptic drugs for control. The antenatal and perinatal periods were uneventful and the birth weight was 2.72 kg. Developmental delay was present and at 15 months of age he could stand and walk with support but had not attained any language milestones. Physical examination revealed microcephaly, flat occiput, hypertelorism, almond shaped eyes, up slanting palpebral fissures, low set ears, bilateral clinodactyly, and ridging of coronal and metopic sutures (Figure 1b). He had increased muscle tone with symmetrically brisk deep tendon reflexes. Right sided testis was not palpable. Complete blood counts, neurometabolic screening, audiograms, ophthalmologic evaluation, echocardiography and sleep EEG were within normal limits. Premature fusion of metopic suture and lateral aspect of bilateral coronal sutures with brachycephaly were observed in skull x-ray and non contrast computed tomography (CT) bone reconstruction scan. Sagittal and lambdoid sutures appeared normal. Right testis was not visualised in the scrotal sac or inguinal canal by ultrasonography. MRI of the brain at 1 year of age showed mildly dilated temporal horn of the right lateral ventricle, but no focal lesions. Cytogenetic studies from peripheral blood revealed a 46,XY,r(14)(p13q32) karyotype (Figure 2b). Mother's karyotype was normal and the father was not available for chromosomal analysis. The mother came for prenatal diagnostic testing during the subsequent pregnancy; the fetal karyotype was normal and the mother later delivered a normal healthy baby.



a) b)

Figure 1 a) Patient with ring chromosome 13 displaying sloping forehead, hypertelorism, bilateral epicanthic folds, broad nasal bridge, short philtrum, wide mouth and protruding upper incisor. b) Patient with ring chromosome 14 showing hypertelorism, almond shaped eyes with up slanting palpebral fissures and low set ears.

Discussion

Ring chromosomes present commonly as intellectual disability and dysmorphism which may be obvious or subtle depending on the observation and acumen of the clinician.

Deletion 13q has a wide phenotypic spectrum depending on the location of the break point relative to chromosomal band 13q32.[5] This syndrome has been classified into three groups. Deletions

	Clinical Features	Kirchhoff *et al.* (n=14)	Su *et al.*	Lance *et al.*	Present case
1	Break Points	All	13q34	13q33.3	13q34
2	Gender	Both	F	F	F
3	Low Birth weight	90.9%	+	+	+
4	Microcephaly	All patients with terminal deletion	+	+	+
5	Intellectual disability	100%	+	+	+
6	Short Stature	2/9 patients with terminal deletion	+	–	–
7	Facial Dysmorphism ('13q facial appearance' as suggested by Kirchhoff *et al.*)				
	High forehead	78.6%	NK	+	–
	Sloping forehead	78.6%	+	NK	+
	Prominent metopic ridge	71.4%	NK	NK	–
	Deep set eyes	64.3%	NK	NK	–
	Hypertelorism	100%	+	+	+
	Inner epicanthic folds	100%	+	+	+
	Strabismus	92.9%	NK	NK	+
	Ear anomalies	100%	+	NK	+
	Broad and prominent nasal bridge	71.4%	+	+	+
	Prominent columella and a short philtrum	57.1%	Short philtrum	NK	+
	Open-mouth appearance	64.3%	+	NK	+
8	Clinodactyly	57.1%	NK	NK	+
9	Foot anomalies (Club foot, Pes cavus, Pes planus)	57.1%	Club foot	NK	Pes planus
10	Hearing anomalies	20%	+	NK	–
11	Seizures	14.3%	–	+	+
	Onset	NK	NA	4Yrs	Day1
	Type	NK	NA	GTCS	GTCS
	Response to treatment	Lasted till age 3Yrs	NA	Refractory	Refractory
12	Behavioural changes	28.6%	–	–	+

NK - Not Known
GTCS - Generalised Tonic Clonic Seizures

Table 1 Phenotypic profile of RC 13 syndrome patients reported by Kirchhoff *et al.*[6], Su *et al.*[8] and Lance *et al.*[11] in comparison with present case.

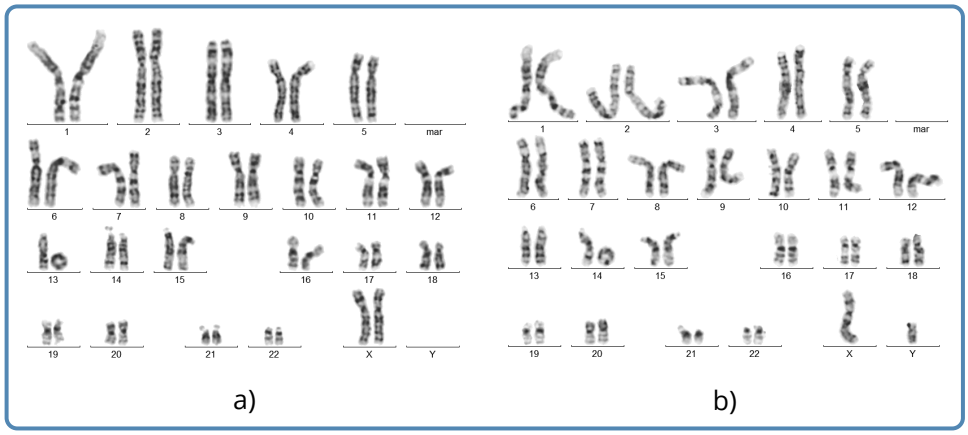


Figure 2 a) Karyotype of patient 1 showing ring chromosome 13; b) Karyotype of patient 2 showing ring chromosome 14.

proximal to q32 and including q32 have been classified under group 1 and 2 respectively, with distinct phenotypes including intellectual disability and growth deficiency, whereas severe intellectual disability, microcephaly with true hypertelorism, frontal bossing, protruding upper incisors and large external ears are frequently found in group 3 with breakpoints at 13q33 and 13q34. Recently, Kirchhoff *et al.* have updated this map by means of high resolution array CGH and have suggested a "13q deletion facial appearance" based on the common dysmorphic features found in a series of 14 patients, regardless of location and size of their deletions [Table 1].[6] Microcephaly is a common feature of individuals with 13q deletions but polymicrogyria is not common.[7] Su *et al.* have recently reported a case of mosaic RC13 [Table 1].[8] Apart from the CNS manifestations, cardiac, renal and genitourinary anomalies are also reported with 13q deletion syndromes.[9–11] Our patient with a deleted band 13q34 presented with early onset epilepsy as the predominant feature. This is a relatively uncommon feature in group 3. With literature review, we could identify only three other cases of group 3 of 13 q deletion syndrome with seizures.[9–11] Two cases reported in the case series by Kirchhoff *et al.* had seizures which lasted until the age of 3 years only.[6] Our patient continued to have seizures at the age of 10. Treatment non-compliance could have contributed to this. On the other hand, our patient bears a close similarity to the case reported by Lance *et al.* who described an 8 year old female child with microcephaly, moderate to severe intellectual disability and uncontrolled epilepsy but without major malformations, harbouring a terminal 13q33.3 deletion.[11] Both cases have a resembling facial profile [Table 1]. We agree with Lance *et al.* in suggesting that the deletion 13q syndrome, group 3 may be more severe than previously indicated and intractable seizures leading to gross cognitive impairment may be considered as a part of the phenotypic spectrum of this group.

Clinically, the RC14 syndrome is characterized by a recognizable phenotype of short stature, distinctive facial appearance, microcephaly, scoliosis, and ocular abnormalities. Almost all patients are intellectually delayed, with aggressive and hyperactive behaviour in some. Seizures occur in all and are usually drug-resistant and predominantly focal type.[12] The facial characteristics include long and sometimes slightly asymmetric face, full cheeks, high forehead, hypoplastic supraorbital ridges, horizontal eyebrows, deep set and down- slanting eyes with short palpebral fissures, hypertelorism, short nose with bulbous tip, long philtrum and small mouth with downturned corners.[12] It is considered that adverse clinical effects like growth retardation, neurologic impairment and facial dysmorphism of RC14 deletions are more pronounced than those of linear 14qter deletions with similar breakpoints.[12–14] Deletion of susceptibility genes during ring formation, position effect of the telomeric end and gene silencing due to spread of inactive state of p arm DNA to q arm are hypothesized mechanisms explaining the clinical manifestations of RC14.[14] One study mentions that in linear terminal 14q deletion syndrome, epilepsy is not included as its component manifestations and seizures are more

likely to be due to ring formation and not the loss of chromosomal material per se.[14] Exact mechanisms pertaining to the severe and drug-resistant seizure disorder are unknown. The reported case had microcephaly, developmental delay, epilepsy and dysmorphic features which are classical presentations of RC14 syndrome but the craniosynostosis seen in the case has not been reported so far with 14q deletion syndrome, to the best of our knowledge. This feature expands the phenotypic spectrum associated with ring 14 syndrome. Since he had the breakpoint at q32 band and 14q32 being the possible region for dysmorphic profile, this unusual trait may be assigned to the 14q32qter region. However delineation of the exact breakpoint by means of FISH or array CGH could not be attempted in our patient.

Ring chromosomes are generally sporadic in occurrence and recurrence in the family is usually low. However, patients with normal reproductive ability should be counselled about the possibility of transmission to the next generation. For our first patient, parental origin of ring 13 was excluded. The paternal karyotype of translocated Y on chromosome 15 was incidental. Most carriers of this translocation have not been reported to have phenotypic consequences and association with reproductive abnormalities is still controversial.[15] Whether this could predispose to ring chromosome formation is at present unknown. Paternal origin of ring 14 could not be excluded in the second patient. However prenatal testing was offered in subsequent pregnancy and the fetal karyotype was found to be normal. Regular follow up was emphasized for both the patients as it is important to assess the natural history, progression of characteristics, and neurodevelopmental achievement.

Conclusion

We have reported here a case of RC13 with unusual presentation of difficult-to-control seizures and a novel case of RC14 with intractable seizures and craniosynostosis. For children with microcephaly, developmental delay and seizures with or without dysmorphism, possibility of ring chromosomes should be kept in mind and karyotype must be an essential part of their evaluation.

References

1. Sigurdardottir, S. *et al.* Clinical, cytogenetic, and fluorescence in situ hybridization findings in two cases of "complete ring" syndrome. *Am J Med Genet* **87**, 384-390 (1999).
2. Guilherme, RS. *et al.* Mechanisms of ring chromosome formation, ring instability and clinical consequences. *BMC Med Genet* **12**, 71-178 (2011).
3. Martin, NJ. *et al.* The ring chromosome 13 syndrome. *Hum Genet* **61** 8-23 (1982).
4. Zollino, M. *et al.* The ring 14 syndrome. *Eur J Med Gen* **55**, 374-380 (2012).
5. Brown, S. *et al.* The 13q-syndrome: the molecular definition of a critical deletion region in band 13q32. *Am J Med Genet* **57**, 859-866 (1995).
6. Kirchhoff, M. *et al.* Phenotype and 244k array-CGH characterization of chromosome 13q deletions: An update of the phenotypic map of 13q21.1-qter. *Am J Med Genet Part A* **149A**, 894-905 (2009).
7. Kogan, JM. *et al.* Interstitial deletion of 13q associated with polymicrogyria. *Am J Med Genet Part A* **146A**, 910-916 (2008).
8. Su, PH. *et al.* Smallest critical region for microcephaly in a patient with mosaic ring chromosome 13. *Genet Mol Res* **12**, 1311-1317 (2013).
9. Huang, C. *et al.* Congenital heart defect and mental retardation in a patient with a 13q33.1-34 deletion. *Gene* **498**, 308-310 (2012).
10. Ballarati, L. *et al.* 13q Deletion and central nervous system anomalies: further insights from karyotype-phenotype analyses of 14 patients. *J Med Genet* **44**, e60 (2007).
11. Lance, EI. *et al.* Expansion of the Deletion 13q Syndrome Phenotype: A Case Report. *Journal of Child Neurology* **22**, 1124-1127 (2007).
12. Zollino, M. *et al.* The ring 14 syndrome: clinical and molecular definition. *Am J Med Genet A* **149**, 1116-1124 (2009).
13. Meschede, D. *et al.* Submicroscopic deletion in 14q32.3 through a de novo tandem translocation between 14q and 21p. *Am J Med Genet* **80**, 443-447 (1998).
14. İncecik, F *et al.* Ring chromosome 14 syndrome presenting with intractable epilepsy: a case report. *Turk J Pediatr* **55**, 549-551 (2013).
15. Onrat, ST *et al.* 46,XX, der(15),t(Y;15)(q12;p11) karyotype in an azoospermic male. *Indian J Hum Genet* **18**, 241-245 (2012).