A case with a ring chromosome 22

Altuğ Koç[1], Kadri Karaer[1], Mehmet Ali Ergün[1], Meral Yirmibeş-Karaoğuz[1]
Derya Kan[1], Ali Cansu[2], Ferda Perçin[1]
Departments of [1]Medical Genetics and [2]Pediatric Neurology, Gazi University Faculty of Medicine, Ankara, Turkey

SUMMARY: Koç A, Karaer K, Ergün MA, Yirmibeş-Karaoğuz M, Kan D, Cansu A, Perçin F. A case with a ring chromosome 22. Turk J Pediatr 2008; 50: 193-196.

Ring chromosome 22, a rare cytogenetic finding, was first described in 1968, and since then about 60 patients have been reported. We describe a new patient with ring chromosome 22 syndrome and discuss the common features of the previously reported cases. Our patient had the major features of this syndrome including mental retardation, hypotonia, motor delay, microcephaly, dysplastic large ears, lack of speech, and hyperactivity disorder. Magnetic resonance imaging findings also revealed an arachnoid cyst, found in the posterior cerebellum. In patients with ring chromosome 22, variable clinical manifestations may be seen due to the size of lost sequences near the telomere. By fluorescent in situ hybridization (FISH) technique, LSI DiGeorge/VCFS/ ARSA locus-specific probes are used to detect deleted sequences. We found that 22q11.2 regions were intact on both chromosomes 22, but 22q13.3 (Arylsulfatase A; ARSA region) was absent in the ring chromosome. As far as we know this is the first reported Turkish patient in the literature.

Key words: ring chromosome 22, autism, dysmorphology, 22q13.3 deletion syndrome, arachnoid cyst.

Ring chromosome 22, a rare cytogenetic finding, was first described by Weleber et al. in 1968[1]. The majority of r22 are formed de novo, but there are rare reports of familial transmission[2]. In these patients, mental retardation, delayed motor development, muscular hypotonia, large ears, epicanthal folds, mood disorder, and lack of speech were the most consistent findings. The phenotypic differences, particularly the growth retardation with microcephaly and severe mental delay, could be the result of a larger deletion size in ring chromosome 22 cases[3].

The most frequently observed features of individuals with ring chromosome 22 overlap with the features of "22q13 deletion syndrome", in which haploinsufficiency of SHANK3/ PROSAP2 is suggested to be responsible[2,4,5]. Ring chromosome 22 patients differ from 22q13 deletion syndrome patients by growth retardation, which is probably the effect of ring instability[6,7]. In the cases of ring chromosome 22, there is usually mosaicism of ring chromosome due to instability[5].

In this report, we present a Turkish child with hypotonia, profound mental retardation, lack of speech, behavioral problems, and minor dysmorphic features. The karyotype revealed a ring 22 chromosome with a 22q13.3 deletion that was confirmed by fluorescent in situ hybridization (FISH).

Case Report

The patient, an eight-year-old boy, admitted to our clinic with mental retardation. He was born to a healthy 39-year-old mother and 42-year-old father. This couple was nonconsanguineous. He had four brothers, one of whom had paralytic poliomyelitis. A brother died during delivery and another brother died after exchange transfusion made for neonatal jaundice. There was also a history of a male stillbirth with an unknown etiology. Pregnancy, delivery, and the neonatal period were uneventful. His birth weight was 3800 g (50-75th centile); length and head circumference were not recorded. He began to sit without support at 1.5 years, started walking at 2.5 years and has not yet talked. There was no sphincter control and his manual ability was poor.

At the time of examination he had mental retardation (IQ 60, WISC-R), behavioral problems such as short attention span, chewing of dirt,

hyperactivity, and aggressive outbursts; he had tried to escape from the house several times. He had been taking haloperidol 24 mg/day for one year to control his behavioral problems.

Physical examination showed height 118 cm (3-10th centile), weight 25 kg (25-50th centile), and occipito-frontal circumference 50 cm (<3rd centile). Microcephaly, brachycephaly, upsweep of frontal hair, mildly prominent forehead, triangular face, broad eyebrows, broad nasal bridge, bulbous tip of nose, prominent columella, crowded teeth, and attached ear lobules were noted (Fig. 1). Bilaterally second fingers deviated to the ulnar side, the fifth finger of the left hand had clinodactyly, and fifth toes also had mediodorsal curve bilaterally. He had gait ataxia and his cognitive functions were severely impaired. Magnetic resonance imaging (MRI) showed an arachnoid cyst found in the posterior cerebellum. The EEG and metabolic screening tests were normal. Routine biochemical and hematological tests were also normal.

Fig. 1. Frontal view of the patient at 8 years showing triangular face, frontal hair upsweep, mildly prominent metopic suture, broad eyebrows, broad nasal bridge and bulbous tip of nose, crowded teeth, and large ears with attached ear lobules.

High resolution Giemsa-banding and C-banding (550 bands) were performed on metaphase chromosomes obtained from peripheral blood lymphocytes of the proband and his parents. FISH was carried out with commercial probes for DiGeorge syndrome (Vysis Inc.), TUPLE 1, consisting of a 110 kb probe covering segments D22S553, D22S609 and D22S942 in 22q11.2 and a LSI-ARSA probe in 22q13.3. Patient's karyotype showed the presence of one chromosome 22 shaped-like ring. The karyotype 46, XY, r(22) was observed in 30 metaphases

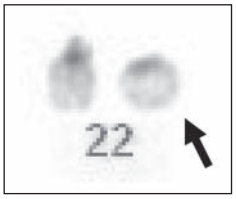

Fig. 2a. Patient's karyotype was found as 46, XY, r(22) in 30 metaphases. Ring structure of derivative chromosome 22 (indicated by arrow) and normal chromosome 22 are demonstrated.

(Fig. 2a). Maternal and paternal karyotypes were normal constitutionally. Results of the FISH test confirmed the presence of a ring chromosome with a 22q13.3 deletion (Fig. 2b).

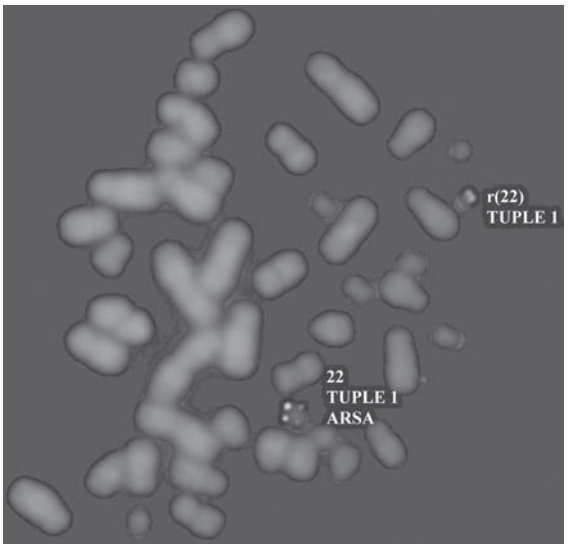

Fig. 2b. LSI TUPLE 1 (red) probe and LSI ARSA (green) control probe hybridized to metaphase cell. Absence of the green signal on ring chromosome 22 indicates the deletion of the LSI-ARSA locus at 22q13.3. r(22): Ring chromosome 22. 22: Normal chromosome 22.

Discussion

Chromosomal rings have been described for all human chromosomes and they are one of the known causes of congenital malformations, even when there is no apparent loss of genetic material[8]. Autosomal ring chromosomes might determine a specific phenotype whatever the chromosome involved; this is known as ring syndrome. Clinical presentation of ring syndrome was defined as severe growth failure together with an almost normal appearance, and was described mainly in patients with large ring chromosomes. The reason for growth failure

is increased ring instability causing cell death[9]. Luciani et al.[9] demonstrated that the majority of metaphases (98-100%) were stable in 17 patients with chromosome r(22). It remains uncertain whether the distinct phenotypes are caused by the loss of a variable amount of chromosomal material or by a cellular mosaicism arising from instability of the ring[3,6,10].

About 60 cases of r(22) have been reported to date[10]. In frequency order, clinical findings of ring 22 syndrome are mental retardation, delayed motor development, hypotonia, large ears, epicanthal folds, mood disorder, lack of speech development, full eyebrows, microcephaly, ataxia, seizures, high-arched palate, syndactyly between 2nd and 3rd toes, flat nasal bridge, hypertelorism, and growth retardation. Most of these common findings were present in our patient, but he had no epicanthus, seizure, high-arched palate, syndactyly or hypertelorism.

Other less frequently reported findings of ring 22 syndrome include clinodactyly of the 5th digit, micrognathia, cleft palate, ocular colobomas, prominent lips, low-set ears, imperforate anus, cardiovascular abnormalities, brain meningiomas, and various MRI findings of the central nervous system[1,11-13].

Patients with behavioral problems and autism were reported[1,15,18]. The association between abnormalities of chromosome 22 and autistic disorder may be the result of mental retardation due to r(22)[14]. In patients with chromosome r(22), the behavioral disorders may increase with age[6]. In this case, mental retardation, lack of speech and behavioral problems were the major complaints. In contrast to previously reported cases, the onset of hyperactivity and aggressive outbursts was in the third year of life and he is now more stable with haloperidol treatment. As mentioned before, anomalies of the central nervous system in r(22) cases have been reported[11]. Additionally, the presented case had an arachnoid cyst in the posterior cerebellum. Although there was no other pathology in the brain MRI of the patient, this finding may be related with ataxic gait of the case, and the follow-up of the patient will be important in this regard.

A different condition, known as 22q13 deletion syndrome, has almost all the features of ring chromosome 22 syndrome. It differs from ring chromosome 22 syndrome only by a tendency to general overgrowth. Unlike 22q13.3 syndrome, ring 22 is characterized by delayed growth (20-24% of individuals) and microcephaly (33%)[6]. All patients with 22q13 deletion syndrome showed some degree of mental retardation, global developmental delay, and absent or severely delayed speech; other common features are generalized hypotonia and normal to advanced growth[4]. Growth retardation of our patient is compatible with ring (22) syndrome.

A few cases of ring chromosome 22 were characterized by molecular studies, and in most of them the segment containing the locus ARSA was deleted[3,14,16-18]. In some r(22) cases, breakpoints with deletion distal to gene ARSA were also reported. In these cases, major clinical findings of ring chromosome 22 syndrome were present[19,20]. In this study, we demonstrated the deletion of 22q13.3 (LSI ARSA).

The association of cryptic 22q deletions with partial trisomies was reported[3]. Praphanphoj et al.[4] found the 22q13 deletion to be associated with a translocation in three of four patients by using multi-telomere FISH assay. No additional chromosomal abnormality to r(22) formation was observed in our case.

Ring chromosome 22 and 22q13 deletion syndromes should be suspected in hypotonic infants or children with growth retardation; children with delayed or absent speech and minor dysmorphic features; and patients with atypical features of FG syndrome without a definite X-linked family history. Giemsa banding and FISH are first-line methods for identification of the etiology, but different approaches are also suggested[4,16,18,20,21]. As in our case, most of the patients with r(22) lack ARSA region and commercial VCFS/DGS FISH probes are suitable for detection of this deletion.

Fertility of male 22q13.3 deletion patients may be affected if the gene Acrosin (ACR) is deleted, which plays a key role in the acrosome-reacted binding of sperm to the zona pellucida and the penetration of sperm into the oocyte[20]. We do not know if ACR was present or deleted in our patient, but the status may be important in reproductive years.

G-ring chromosome in a male Turkish patient was reported in 1970 by Say et al.[22], but the patient had Chédiak-Higashi syndrome, and

the origin of G-ring was not identified, so the presented case is the first reported Turkish child with ring 22 syndrome.

The growth retardation of our patient helped us to rule out 22q13 deletion syndrome clinically, whereas karyotype confirmed the diagnosis of ring 22 syndrome. FISH analysis revealed 22q13 deletion. We conclude that clinical genetics combined with routine cytogenetic and molecular genetic studies have a great impact in diagnosis of discrete syndromes.

REFERENCES

1. Ishmael HA, Cataldi D, Begleiter ML, Pasztor LM, Dasouki MJ, Butler MG. Five new subjects with ring chromosome 22. Clin Genet 2003; 63: 410-414.
2. Kosztola´nyi G. Does "ring syndrome" exist? An analysis of 207 case reports on patients with a ring autosome. Hum Genet 1987; 75: 174-179.
3. De Mas PD, Chassaing N, Chaix Y, et al. Molecular characterization of a ring chromosome 22 in a patient with severe language delay: a contribution to the refinement of the subtelomeric 22q deletion syndrome. J Med Genet 2002; 39: e17.
4. Praphanphoj V, Goodman BK, Thomas GH, Raymong GV. Cryptic subtelomeric translocations in the 22q13 deletion syndrome. J Med Genet 2000; 37: 58-61.
5. Wong AC, Nong Y, Flint J, et al. Molecular characterization of a 130-kb terminal microdeletion at 22q in a child with mild mental retardation. Am J Hum Genet 1997; 60: 113-120.
6. MacLean JE, Teshima IE, Szatmari P, Nowaczyk MJ. Ring chromosome 22 and autism: report and review. Am J Med Genet 2000; 90: 382-385.
7. Pezzolo A, Gimelli G, Cohen A, et al. Presence of telomeric and subtelomeric sequences at the fusion points of ring chromosomes indicates that the ring syndrome is caused by ring instability. Hum Genet 1993; 92: 23-27.
8. Phelan MC, Curtis Rogers R, Saul RA, et al. 22q13 deletion syndrome. Am J Med Genet 2001; 101: 91-99.
9. Luciani JJ, de Mas P, Depetris D, et al. Telomeric 22q13 deletions resulting from rings, simple deletions, and translocations: cytogenetic, molecular, and clinical analyses of 32 new observations. J Med Genet 2003; 40: 690-696.
10. Battini R, Battaglia A, Bertini V, et al. Characterization of the phenotype and definition of the deletion in a new patient with ring chromosome 22. Am J Med Genet 2004; 130A: 196-199.
11. Delcan J, Orera M, Linares R, Saavedra D, Palomar A. A case of ring chromosome 22 with deletion of the 22q13.3 region associated with agenesis of the corpus callosum, fornix and septum pellucidum. Prenat Diagn 2004; 24: 635-637.
12. Chen CP, Chern SR, Chang TY, et al. Prenatal diagnosis of mosaic ring chromosome 22 associated with cardiovascular abnormalities and intrauterine growth restriction. Prenat Diagn 2003; 23: 40-43.
13. McClarren J, Donnenfeld AE, Ravnan JB. Prenatal diagnosis of an unexpected interstitial 22q11.2 deletion causing truncus arteriosus and thymic hypoplasia in a ring 22 chromosome derived from a maternally inherited paracentric inversion. Prenat Diagn 2006; 26: 1212-1215.
14. Nesslinger NJ, Gorski JL, Kurczynski TW, et al. Clinical, cytogenetic, and molecular characterization of seven patients with deletion of chromosome 22q13.3. Am J Hum Genet 1994; 54: 464-472.
15. Wilson HL, Wong AC, Shaw SR, et al. Molecular characterization of the 22q13 deletion syndrome supports the role of haploinsufficiency of SHANK3/PROSAP2 in the major neurological symptoms. J Med Genet 2003; 40: 575-584.
16. Gustavson KH, Arancibia W, Eriksson U, Svennerholm L. Deleted ring chromosome 22 in a mentally retarded boy. Clin Genet 1986; 29: 337-341.
17. Frizzley JK, Stephan MJ, Lamb AN, et al. Ring 22 duplication/deletion mosaicism: clinical, cytogenetic, and molecular characterization. J Med Genet 1999; 36: 237-241.
18. Ning Y, Rosenberg M, Biesecker LG, Ledbetter DH. Isolation of the human chromosome 22q telomere and its application to detection of cryptic chromosomal abnormalities. Hum Genet 1996; 97: 765-769.
19. Borovik CL, Muller R, Demarchi AL, et al. Characterization of a ring chromosome 22 by molecular genetics. Einstein 2003; 1: 113-116.
20. Prasad C, Prasad AN, Chordirker BN, et al. Genetic evaluation of pervasive developmental disorders: the terminal 22q13 deletion syndrome may represent a recognizable phenotype. Clin Genet 2000; 57: 103-109.
21. De Vries BB, Bitner-Glindzicz M, Knight SJ, et al. A boy with a submicroscopic 22qter deletion, general overgrowth, and features suggestive of FG syndrome. Clin Genet 2000; 58: 483-487.
22. Say B, Tuncbilek E, Yamak B, Balci S. An unusual chromosomal aberration in a case of Chediak-Higashi syndrome. J Med Genet 1970; 7: 417-421.