A case with a ring chromosome 22

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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 transmission². 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 cases³.

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 responsible²,⁴,⁵. Ring chromosome 22 patients differ from 22q13 deletion syndrome patients by growth retardation, which is probably the effect of ring instability⁶,⁷. In the cases of ring chromosome 22, there is usually mosaicism of ring chromosome due to instability⁵.

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). 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. 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. 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.

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. 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. Luciani et al. 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.

About 60 cases of r(22) have been reported to date. 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.

Patients with behavioral problems and autism were reported. The association between abnormalities of chromosome 22 and autistic disorder may be the result of mental retardation due to r(22). In patients with chromosome r(22), the behavioral disorders may increase with age. 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. 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%) in 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. 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. 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. In this study, we demonstrated the deletion of 22q13.3 (LSI ARSA).

The association of cryptic 22q deletions with partial trisomies was reported. Prapanphoj et al. 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. 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. 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., 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