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CASE REPORT

Partial 21q monosomy due to 21q inversion and 21 Chromosome Ring: Two Case Reports

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ABSTRACT

Background: Children with multiple congenital anomalies are usually evaluated in search of a known syndrome with chromosomal, monogenic, or multifactorial causes. Aneuploidies of chromosome 21 are the most common chromosomal abnormalities in humans. 21q deletion syndrome is a very rare genetic disorder caused by the absence of the genetic material in the long arm of chromosome 21, with variable clinical features.

Aim: to report two cases of 21 deletion syndrome produced by two different mechanisms with variable clinical manifestations at early ages.

Case 1: 10-year-old boy with growth retardation, intellectual disability, microcephaly, facial dysmorphism, joint stiffness, scoliosis. Karyotype 45, XY, -21. Mother with 46, XX, inv(21)(p12q22.1). On chromosome microarray analysis, we found a partial 18p deletion and a 21q deletion.

Case 2: 11-weeks male with boy with growth retardation, global developmental delay, microtia, short neck, scoliosis, hemivertebrae, and interatrial communication. Chromosome microarray analysis showed a partial deletion of 21q secondary to a 21-chromosome ring.

Discussion: There are different mechanisms of 21 deletion syndrome and a variety of clinical manifestations and severity depending on the rearrangements and other chromosomes involved.

Conclusion: both patients have growth retardation and intellectual disability, but differ in facial dysmorphisms and the presence of other congenital malformations such as cardiac and genitourinary. The correct approach of multiple congenital anomalies and intellectual disability allows for an appropriate diagnosis and genetic counseling.

Introduction

Children with multiple congenital anomalies (MCAs) are usually evaluated in search of a known syndrome, and nearly 50% of them never receive a diagnosis[1]. Chromosome microarray analysis (CMA) helps in the identification of chromosome abnormalities in different disorders, and it is now the standard evaluation for individuals with multiple congenital anomalies and/or neurodevelopmental disorders[2].

Structural variations (SVs) are defined as a difference in the DNA copy-number, orientation, or location of large genomic segments and have been recognized as an important cause of intellectual disability and multiple congenital abnormalities (ID/MCA)[3].

Aneuploidies of chromosome 21 are the most common chromosomal abnormalities in humans, with a low percentage of partial trisomies or monosomies[4]. 21q deletion syndrome is a very rare genetic disorder caused by the absence of the genetic material in the long arm of chromosome 21[5] with variable clinical features that include intrauterine and postnatal growth retardation, microcephaly, prominent occipital, facial dysmorphism (small and upslanting palpebral fissures, prominent nasal bridge with a wide nose and large ears), and intellectual disability. They can also present with brain and cardiac malformations[6]. Three regions have been described depending on the size and location of the deletion; region 1 ranges from 21q11.2-q22.11 (from centromere to 31.2 Mb and about 50 genes), the second region from 21q22.11-q22.12 (31.2 to 36 Mb and about 80 genes), and region 3 from 21q22.12-q22.3 (36 to 37.5 Mb to the telomere with more than 130 to close genes[7]. Clinically, patients with deletions in regions 1 and 2 usually present with a more severe phenotype, and patients with deletions in region 3 have a milder phenotype[5].

The loss of genetic material is due to three different mechanisms. A terminal/interstitial deletion, where a chromosomal break occurs, and a segment is subsequently lost. Deletions involving the critical 21q22 region typically present the most severe phenotypes[8]. The second is a 21-ring due to breaks at both ends of the chromosome (p and q), followed by the fusion of the break points to form a ring. In addition to the loss of telomere material, the ring is inherently unstable during mitosis, leading to dynamic mosaicism (cells with 45,X, -21 or cells with multiple rings), which exacerbates the clinical picture. And the last one is the 21q isochromosome that occurs when the chromosome divides transversely instead of longitudinally during meiosis or mitosis, resulting in monosomy of the short arm (21p) and trisomy of the long arm (21q). Although there is an "excess" of q material, the absence of regulatory regions and the overall genomic imbalance produce a clinical spectrum that often overlaps with pure 21q deletion or Down syndrome, depending on the predominant cell line[9].

In this paper, we present two different cases of 21 deletion syndrome secondary to two structural aberrations, one 21 chromosome ring and one derivative from a maternal 21q inversion, highlighting the different clinical manifestations dependent on the lost genomic material.

Case 1

A 10-year-old male product of the second pregnancy of a young and healthy non-consanguineous couple, but from the same town. The first pregnancy ended in abortion. Maternal grandmother has a history of multiple miscarriages. Referred to as a normal pregnancy, delivered at 37 weeks with a weight of 2kg (P<1, Z-2.65), height 39cm (P<1, Z-5.22), 5 minutes APGAR of 8. Send to medical genetics for low weight and height, facial dysmorphism, short neck, aortic valve stenosis, and spasticity of upper and lower limbs.

A karyotype was performed at 15 months with 45, XY, -21 result (Figure 1A). Physically with microcephaly, trigonocephaly, high palate, downslanted palpebral fissures, short philtrum, short neck, dorsal xiphosis, inguinal hernias, short penis, adductus thumbs, hyperreflexia, and global developmental retardation. On brain CT scan, cortical atrophy was observed. There was no option for another type of studies at that time.

He lost follow up until 9 years when he returned with a weight of 13.7kg (P<1, Z-8), height of 112cm (P<1, Z-4.3), hypertonia, microcephaly, upslanting palpebral fissures, prominent brow ridges, anteverted nares, auricles with posterior rotation, absence of teeth, short neck, asymmetric chest, heart murmur, scoliosis, clinodactyly, cutaneous syndactyly and bilateral cryptorchidism (Figure 1B). Mother had a third pregnancy with an ultrasound that reported multiple malformations. An amniocentesis was offered and reported 45, XY, -21. They decided to interrupt the pregnancy. With this second monosomy, a karyotype was performed on both parents, and the mother has a karyotype of 46, XX, inv(21)(p12q22.1) (Figure 1C). We also performed FISH analysis which reported 21(TMPRSS2/ERG)x2.

Figure 1A-C. Case 1 phenotype and karyotypes.

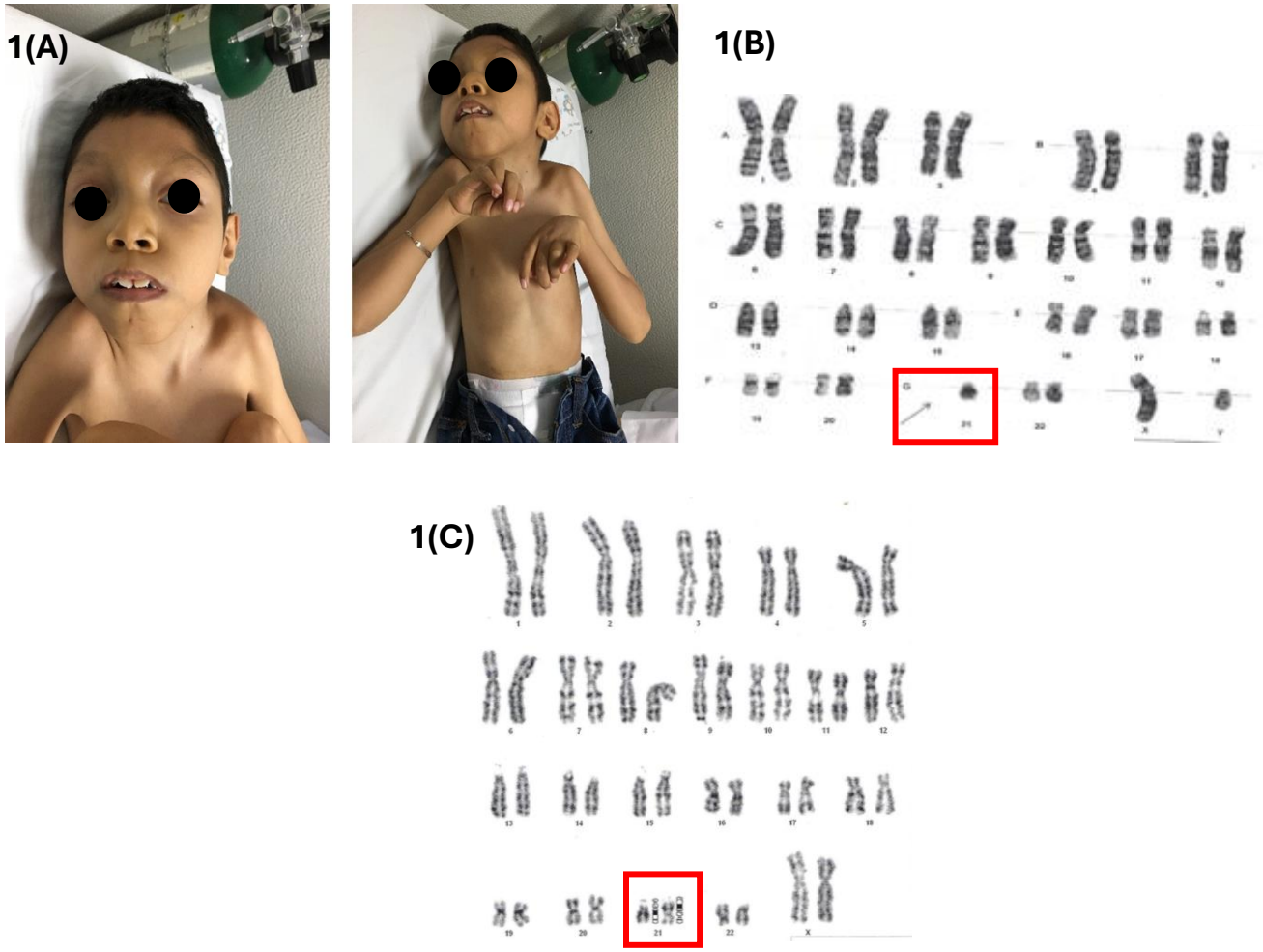

Figure 1(A) Patient phenotype; 1(B) G-banded karyotype; 1(C) Mother's G-banded karyotype.

Initiated with generalized epilepsy at 10 years. We could perform a CMA at 10 years with the following result: 18p11.32p11.21 (136,227_15,170,636) x1, 21q11.2q21.3 (15,016,486_30,576,097) x1.

Case 2

A 11-week-old male, the fourth pregnancy of a healthy non-consanguineous couple with two previous abortions. On prenatal control, ventriculomegaly, a single umbilical artery, and intrauterine growth restriction were detected. C-section was performed at 37.5 weeks, weight 1850g (P<1, Z-2.92), height 43cm (P<1, Z-3.56), head circumference (HC) 31cm (P<1, Z-3.72), 5 minutes-APGAR of 9. Because of the prenatal diagnosis, we performed a renal ultrasound, which was reported as normal. He was also evaluated by the cardiology department and was found to have a patent ductus already closed.

At physical examination, the weight was 3.93kg (P2, Z-2) and height 48cm (P<1, Z-4.2), right microtia with external auditory canal stenosis, dysplastic auricles, bilateral preauricular appendix, short neck, and scoliosis. No neurodevelopmental retardation.

On the follow-up, right hypoacusis and interatrial communication were diagnosed. Chest x-ray showed the presence of T6-T8 hemivertebrae and rib fusion.

For multiple congenital malformations, a CMA was made and reported 21q22.3(42,743,565_46,673,449)x1 (Figure 2A).

On the last visit at 21 months, he persisted with short stature, microcephaly (HC 42cm, P<1, Z-5.9), heart murmur, moderate hypoacusis, late speech, and scoliosis. A karyotype was performed and reported 46, XY, r(21)(p13q22) (Figure 2B). With the history of miscarriages, we ordered karyotypes in both parents; the result is pending.

Figure 2A-B. Case 2 Chromosomal Microarray (CMA) and karyotype.

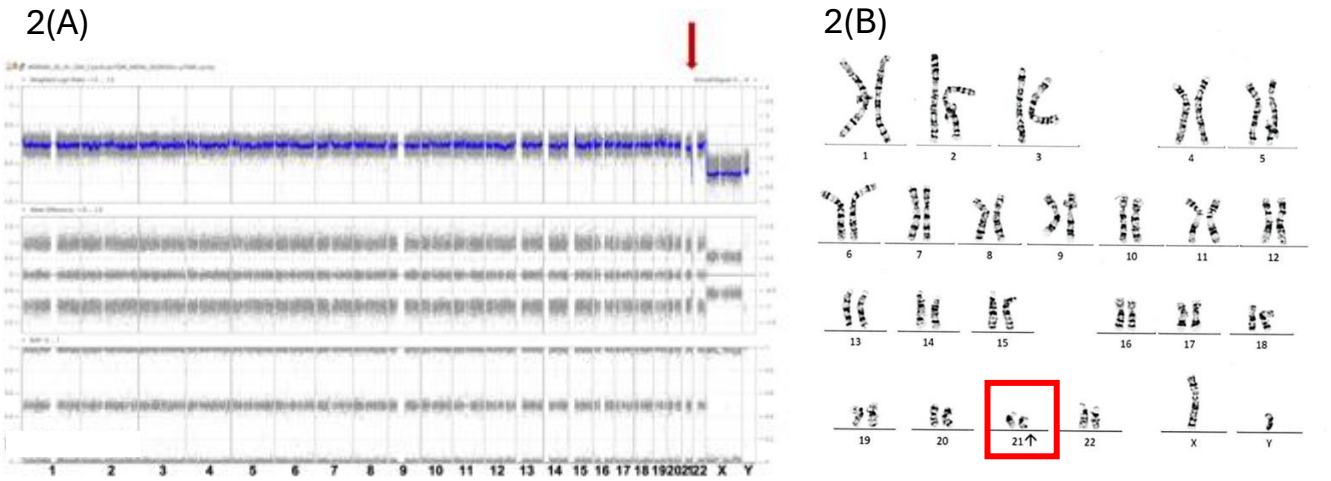

Figure 2(A) CMA 21q22.3(42,743,565_46,673,449)x1; 2(B) G-banded karyotype.

Discussion

Partial deletion of the long arm (q) in chromosome 21 is an infrequent chromosome abnormality that occurs in <1/1,000,000 births. Most cases of 21q deletions are attributed to chromosomal abnormalities like translocations, deletions, and duplications involving chromosomes other than 21[10].

Most of these of these partial monosomies are *de novo* reported on the cytogenetic level, and only a few are submicroscopic deletions[11]. A comprehensive analysis of intrachromosomal duplications and breakpoints on human chromosome 21 revealed that multiple copies of sequences in key regions contain a large, segmented duplication with 96% identity between its proximal and distal portions. These regions are the origin of various breakpoints, revealing that these are not randomly distributed but rather clustered in specific areas of the chromosome. A significant relationship exists between duplicated regions and the propensity for chromosomal rearrangements, suggesting shared molecular mechanisms[12].

Partial chromosome 21 monosomy is a rare human disease with variable clinical appearances due to different genomic content resulting in phenotypes including intellectual disability, brain dysgenesis, dysmorphic features (microcephaly, short neck, epicanthic folds, flat nasal bridge, low-set/malformed ears, highly arched palate, and transverse palmar crease), heart and/or renal defects[11].

Clinical symptoms can differ significantly by the mechanism of 21 deletion, size, and location[13]. The majority of existing research has focused on deletions within a specific 31.2 Mb region (21q11.2-q22.11), which encompasses approximately 50 genes[14]. While simple deletion and 21 ring usually present pre- and postnatal restriction and language alteration[10], patients with isochromosome might have short or normal stature. About malignancy, the 21q isochromosome has a higher risk of developing leukemia. The mechanisms might have mental retardation but are most severe in mosaic 21 ring[9].

The result of karyotype in patient 1 caught our attention because 21 monosomy is not compatible with life probably because of the dysregulated expression of 249 genes that are part of the embryo implantation universe[15]. But it was not until CMA that we found out that there was another chromosome involved. OMIM reported 14 morbid genes deleted on 18p11.32p11.21 (*THOC1, TYMS, SMCHD1, LPIN2, TGIF1, LAMA1, NDUFV2, APCDD1, PIEZO2, GNAL, TUBB6, AFG3L2, PSMG2, MC2R*) and 6 morbid genes on 21q11.2q21.3 (*NRIP1, USP25, TMPRSS15, MRPL39, JAM2, APP*).

On the DECIPHER database, we found only 2 cases with a similar size of deletion (15.3Mb) but with more genes involved (nearly 200) in chromosome 18. Clinical manifestations of these cases were abnormal facial shape, learning disability, anterior hypopituitarism, short stature, and moderate intellectual disability. About chromosome 21, cases reported were larger than ours (Figure 3A-B).

Figure 3 A-B. Information obtained from the DECIPHER database on chromosomes 18 and 21.

Figure 3A. 18p11.32p11.21 on DECIPHER, morbid genes reported and similar cases (arrows).

Figure 3B. 21q11.2q21.3 on DECIPHER, and morbid genes reported.

According to Errichiello et al, the 21q deletion reported is on subregion 1, which compromises the centromere to approximately 21 Mb, associated with intellectual disability and a severe phenotype. They also mentioned that not all patients with proximal deletions have a more severe phenotype[16].

18p deletion syndrome is caused by a deletion of all or part of the short arm of chromosome 18, with an estimated incidence of 1:50,000 live-born infants. Common features include different degrees of intellectual disability, postnatal growth retardation, microcephaly, a round face, epicanthic folds, ptosis, downward-sloping corners of the mouth, dysplastic ears, and a short neck. They can also present congenital heart defects or brain malformations[17].

In Table 1, we provide a comparison of clinical manifestations in both syndromes. We can attribute high palate, teeth problems, and micropenis to the 18p deletion; microcephaly, spasticity of upper and lower limbs, and aortic valve stenosis to the 21q deletion syndrome.

Table 1. Clinical manifestations

	Deletion 18p(# 146390 OMIM)	Deletion 21q(ORPHA574)	Case 1
Growth	Short stature Low birth weight	Intrauterine and postnatal growth retardation	Short stature Low birth weight
Head/Neck	Round face Large, dysplastic ears Hypertelorism Broad nasal bridge Upturned nostrils Micrognathia High palate Misaligned teeth Redundant neck skin	Microcephaly Prominent occiput Up or down-slanted small palpebral fissures Prominent nasal bridge with a broad nose Large ears	Microcephaly, trigonocephaly Ears with posterior rotation High palate Upslanted palpebral fissures Short philtrum Anteverted nares Absence of teeth Short neck
Genitourinary	Micropenis Hypoplastic testes Gonadal dysgenesis Cryptorchidism		Inguinal hernias Short penis Cryptorchidism
Skeletal	Clinodactyly	Stiff joints with unusual position Abnormal muscle tone	Spasticity of upper and lower limbs Dorsal xiphosis, scoliosis Adductus thumbs Clinodactyly Cutaneous syndactyly
Neurologic	Developmental delay Mental retardation Dystonia	Structural brain malformations (cerebral atrophy, cortical dysplasia, and corpus callosum dysgenesis) Severe intellectual deficit Seizures	Global developmental retardation Cortical atrophy Hypertonia Hyperreflexia
Cardiovascular		Heart defects (patent ductus arteriosus, septal defects)	Aortic valve stenosis

Comparison of clinical manifestations of case 1 versus classical deletion 18p and deletion 21q syndromes.

Wakabayashi et al reported in 2025 the case of a boy with partial monosomy 18p and 21q due to a paternal reciprocal translocation. The clinical manifestations were cleft lip and palate detected prenatally, facial dysmorphisms that included depressed nasal bridge, upslanted palpebral fissures, hypertelorism, widely spaced nipples, inguinal hernia, micropenis, and overlapping fingers. He was diagnosed with lobar holoprosencephaly (HPE) and syndrome of inappropriate antidiuretic hormone. They attribute most of the clinical manifestations as HPE to chromosome 18p deletion, but the 21q11.2-q21.3 deletion may have an effect on brain development and developmental delay, as evidenced by the presence of an inguinal hernia and widely spaced nipples. In our case, we found more facial dysmorphism as well as microcephaly and congenital heart malformation, possibly secondary to 21q deletion. They also made a comparison with other 9 cases, all apparently derived from translocations[18]. In our case, we did not find any translocation involving 18 and 21, the aberration was a maternal 21q pericentric inversion, which is relatively frequent (about 1–2%) and can lead to imbalanced offspring with zygotes either with a partial trisomy or monosomy recombinant chromosomes. Oliveira et al reported the first case of partial 21 monosomy associated with a chromosome pericentric inversion in which the proband and her mother exhibit a consistent phenotype attributed to the 1.7 Mb interstitial deletion. Both individuals possess moderate intellectual disability with severe social challenges[11]. There are other cases in which 21 pericentric inversions cause infertility as a unique manifestation[19]. In our case, the deletion comprises 15,560 Mb in 21q11.2q21.3, bigger than the one reported by Oliveira. On the DECIPHER database, there are 5 other cases (285987, 285691, 317441, 501702, 472608) that involve this amount of Mb, only 3 describe the phenotype (global developmental delay, microcephaly), but there is no information about the mechanism.

In case 2, we initiated with CMA because of microcephaly, growth retardation, and facial dysmorphism. OMIM reported 23 morbid genes (*WDR4, CBS, CRYAA, SIK1, HSF2BP, PDXK, CSTB, TRAPPC10, AIRE, ICOSLG, PFKL, CFAP410, TSPEAR, ITGB2, ADARB1, COL18A1, SLC19A1, COL6A1, LSS, COL6A2, FTCD, MCM3AP, PCNT*) on 21q22.3qter. On the DECIPHER database, there are 3 more cases with the same amount of Mb involved (366645, 414037, 504057), with features like global developmental delay, hypotonia, scoliosis, growth retardation, and delayed speech. Due to the partial monosomy, we requested a karyotype and found the 21-chromosome ring. McGinniss et al in 1992 reported 11 cases of chromosome 21 ring, 6 were non-familial cases, all of them with significant features like developmental delay, short stature, microcephaly, bilateral epicanthal folds, short neck, and small or simplified ears[20]. In our report, the patient has short stature, microcephaly, and microtia as these patients but also a heart congenital malformation and vertebral anomalies. Pardal et al. in 2004 described patients with rib malformation[21], similar to our patient.

The 21q microdeletion detected in our patient involves a relatively smaller region without the involvement of the Down syndrome critical region (DSCR)[22], and other reports suggested that small deletions could result in mild or no clinical consequence[16] but in our case, the patient has sufficient malformations to support the contribution of the partial monosomy.

About the mechanism of 21 chromosome ring formation, McGinniss et al also studied the same 11 cases and found that 9 of them were formed by breakage and reunion of the short and long arms, resulting in partial monosomy of distal 21q without a history of isochromosome or translocation[20]. In our case, parents' karyotypes are pending, but the history of previous miscarriage may raise suspicion of chromosomal abnormalities in the parents.

Conclusion

The approach of patients with intellectual disability and congenital malformations includes the performance of cytogenetics, CMA if possible, or karyotype. In our first case, the 21-monosomy found on the karyotype was what attracted the most attention because it is not usually compatible with life. Unfortunately, no further studies were available at that time, and we assumed that the severity of the phenotype was secondary to 21-monosomy until we could perform the array. Surprisingly, the 18p deletion syndrome caused the severe dysmorphic features. In the second case, the patient was also studied for the presence of congenital malformations, but he was initially approached with CMA that showed the 21-monosomy, and then, the karyotype developed the 21-ring.

Conflicts of Interest Statement

The authors have no conflicts of interest to declare.

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