Derivative chromosome 7 in a newborn with hypotelorism, cleft palate, agenesis of corpus callosum and semilobar holoprosencephaly

Simão L.[1]; Serafim S.[1]; Brito F.[1]; Ventura C.[1]; Scortenschi E.[2]; Santos V.[2]; Correia H.[1]

[1]Unidade de Citogenética, Departamento de Genética Humana, Instituto Nacional de Saúde Dr. Ricardo Jorge,I.P.,Lisboa; [2]Serviço de Medicina Intensiva Pediátrica e Neonatal, Centro Hospitalar Universitário do Algarve, Unidade de Faro.

INTRODUCTION

For any autosomal structural rearrangement in which cytogenetic imbalance can be demonstrated, serious phenotypic abnormality is highly likely.
These rearrangements can cause disease by physically disrupting genes or altering their regulatory environment. Derivative chromosomes are structurally rearranged chromosome generated by a rearrangement involving two or more chromosomes or rarely by multiple rearrangements within a single chromosome.
Often, it is not possible at microscopic level to distinguish if a chromosomal anomaly involves one or more than one chromosome. In these cases, the parents study is fundamental and is usually the first line of study.
Holoprosencephaly (HPE) is the most common malformation affecting the cleavage of the developing forebrain and typically results in neurocognitive impairment with accompanying midline facial anomalie[1]. Partial monosomy of the long arm of chromosome 7 has been characterized by wide phenotypic manifestations, but HPE, hypotelorism and microcephaly has frequently been associated with this chromosomal deletion[2,3].

CLINICAL REPORT

We report a female newborn with multiple anomalies.

A 23-year-old pregnant woman was referred for prenatal service after a 20 weeks of gestation ultrasonography (USS) that reveals a slightly diminished relation cephalic perimeter/abdominal perimeter and low weight, without other anomalies. USS at 32rd weeks of gestation revealed moderate ventricular dilatation, microcephaly, intrauterine growth restriction (IUGR), and normal umbilical arteria. The parents were young and healthy, with a healthy 16 mouths baby, and no relevant family history.

Delivery was at 35 weeks with severe oligoamnios. Microcephaly (CP 25.1cm, <P3), low birth weight (1730g, P3-10), and low birth length (39.5cm, <P3) were present.

Complete medium lip and cleft palate with nasal depression, anal fistula, hypotelorism were observed.

USS reveals agenesis of the corpus callosum, thalamic fusion and fusion of the lateral ventricles in the frontal region suggestive of semilobar HPE.

Fever suggesting central hyperthermia was observed. Seizures, with tremors of the lower limbs, facial myoclonias, chew movements and nistagmus were described since the eighth day. Hypotonia was present.

In addition, was diagnosed probable diabetes insipidus: hypernatraemia, polyuria, and low urinary density. Results of pelvis and abdominal USS were normal and echocardiogram reveals foramen with interauricular communication. Sepsis was developed at day 14 followed by death at day 18 in consequence of seizures and respiratory insuficiency.

Cytogenetic analysis revealed an abnormal chromosome 7qter as a result of an unbalanced segregation of a maternal reciprocal translocation t(7;19), with breakpoints at 7q36.1 and 19q13.42. The newborn karyotype is 46,XX,der(7)t(7;19)(q36.1;q13.42)mat. The patient presented a partial trisomy of the region 19q13.42→qter and a partial monosomy of the region 7q36.1→7qter.

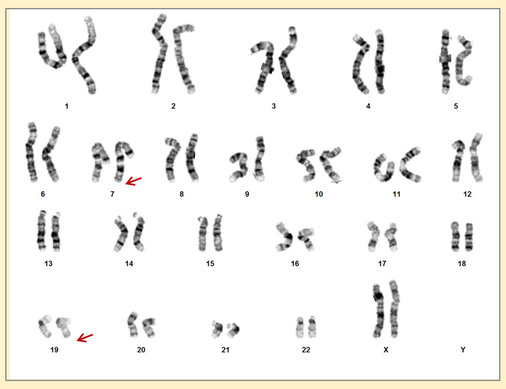

Figure 1 – Karyotype with indication of the two breakpoints (red arrows) of the translocation (7;19)

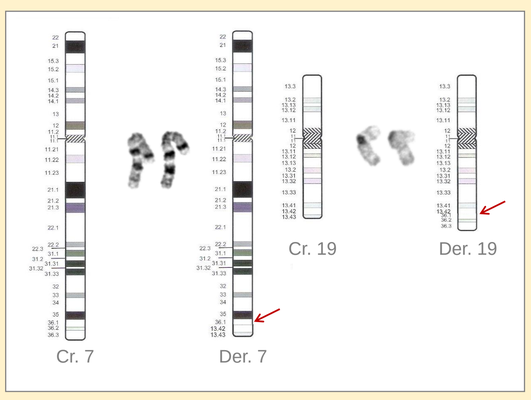

Figure 2 – Ideograms and partial metaphases of the two chromosomes 7 and 19 showing the breakpoints of the translocation

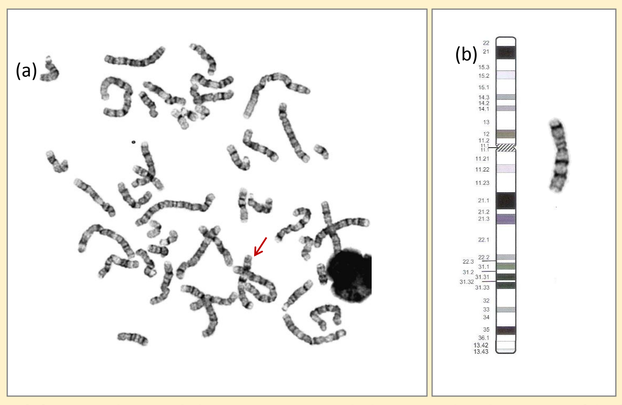

Figure 3 – (a) Metaphase of the case reported showing the derivative (der) chromosome 7 (red arrow); (b) the ideogram and partial metaphase of the der(7)

Table -Clinical findings present (X) in patients with del(7qter) (cases 1-13) and dup(19qter) (cases 15-25) comparatively with those present in the reported case (case 14). In the column of each case, different colors encompass different ages: prenatal; newborn/liveborn; months of the child; years of the child.

Cases (references)	1[4]	2[5]	3[6]	4[7]	5[7]	6[8]	7[9]	8[1]	9[1]	10[7]	11[4]	12[2]	13[10]	14	15[11]	16[12]	17[13]	18[14]	19[15]	20[16]	21[17]	22[18]	23[19]	24[20]	25[21]
	7q breakpoints														19q breakpoints										
Breakpoints	36	36.1	36.1-	36	36.1	36	36.1	SHHMu	36	36	SHHMu	36.2	36.2-qter	7q36.1 -qter*	13.3	13.3	13.2	13.3-qter	19.3	13.3	13.42	13.42	13.4	13.33	13.3
TOP weeks / Born	16	19	23				38				term		39		15		term		term		39			term	38
Age (days/months/years)				2m	3m-1y	18 m	2y	2y	3y	5y	child	13y	13y	18d		7d	10d	Live born	15d -1m	20m	2y	5y	child	8y	14y
IUGR	x	x												x	x										x
Low birth weight														x		x				x					x
Low birth length												x	x	x		x				x					x
Low cephalic perimeter								x	x		x	x	x	x		x				x	x				
Nuchal edema															x			x							
Omphalocele	x																								
Oligoamnios			x											x											
Agenesis of the *corpus callosum*	x			x													x		x						
Holoprosencephaly			x		x			x	x	x															
Cerebral atrophy																				x			x		
Microcephaly				x	x	x	x	x	x	x				x		x					x				x
Growth and psychomotor retardation					x	x						x					x		x	x	x	x	x	x	x
Intellectual disability						x	x					x							x		x	x		x	x
Short stature							x				x		x											x	x
Hypotonia												x		x			x		x		x	x			x
Seizures							x							x					x	x				x	x
Craniofacial features			x		x	x							x				x		x		x		x		
Large bossed forehead												x									x	x	x		
Midface hypoplasia				x	x		x		x	x											x				
Coloboma						x					x		x				x								
Microphthalmia					x						x		x												
Nystagmus													x	x					x						x
Other eye abnormalities						x						x	x										x		x
Hypertelorism																			x					x	x
Hypotelorism							x	x	x					x								x			
Low set ears															x		x				x		x		x
Other ear malformations													x					x				x		x	x
Small nose															x	x	x								x
Nasal bridge anomalies				x	x		x		x				x	x	x	x	x	x			x	x			x
Cleft lip and palate					x									x		x									
Down turn mouth										x			x			x		x						x	
Agenesis of central maxillary incisors					x		x			x	x		x												
Micrognathia															x				x						x
Short neck												x			x			x			x	x		x	x
Congenital heart defects	x													x	x	x	x	x		x	x				x
Anomalies of the genito-urinary tract	x				x		x								x		x	x							x
Anomalies of the gastro-intestinal tract							x							x			x		x						
Scoliosis/ vertebral anomalies			x								x	x													
Hemivertebra			x																						
Sacral agenesis/ Curradino syndrome spectrum		x				x	x					x													
Tappering fingers																						x		x	
Clinodactyly / Bilateral fifth finger clynodactyly							x								x		x		x				x	x	
Probable diabetes insipidus														x											

DISCUSSION

- We report a derivative chromosome 7 resulting from a unbalanced translocation (7;19), resulting in a partial trisomy of the region 19q13.42→qter and a partial monosomy of the region 7q36.1→7qter.
- The terminal 7qdel encompasses several OMIM genes, including the Sonic Hedgehog (*SHH*) gene at 7q36.3, involved in development, and described as associated to HPE3(OMIM#142945), hypotelorism and nasal depression, witch agree with the clinical report of the present case (Table I). However, is not often reported in newborns.
- To our knowledge, there is only one similar and previous case of der(7)t(7q;19q)(q36.1;q13.43) described, in a fetus who presented IUGR and severe sacral agenesis, that may occur in isolation or as part of the Currarino triad of anorectal, sacral, and presacral anomalies[5]. The frequent association in this region deletions and HPE and Currarino Syndrome(OMIM#176450) is probably due to this region encompasses the *SHH* gene and the *HLXB9* gene at 7q36.3[2,4].
- Although partial monosomy of the terminal long arm of chromosome 7 has been characterized by wide phenotypic spectrum, HPE, microcephaly, hypotelorism, midface hypoplasia, other craniofacial dysmorphisms, maxillary anomalies and sacral agenesis are frequently described. Eye abnormalities, short stature, and agenesis of both central maxillary incisors have been associated with this region deletion[10].
- Unbalanced rearrangements of chromosome 19q, which has a great gene density have been rarely reported, suggesting that genetic material of this chromosome is essential for survival[14].
- Thus, partial trisomy 19q is a rare and severe condition, and has been described associated with low birth weight, growth retardation and psicomotor retardation, seizures, dysmorphic facial features, short neck, clynodactyly, heart malformations, anomalies of the genitor-urinary and gastrointestinal tract and most cases result from unbalanced translocations with variable phenotypes[11,17,20].
- Most of previously described distal 19q partial trisomies were detectable by conventional cytogenetic techniques, but molecular techniques allowed to show that the 19q13.42q13.43 region comprises several genes and is dense in pseudogenes and microRNAs, which are potent regulators of gene expression[15,20].
- The case herein reported presents some of the most common features of 7q36 partial monosomy and 19q terminal trisomy, although some of them are present in both conditions, as IUGR, microcephaly and facial anomalies.
- However, HPE and hypotelorism are more associated to del7qter, while seizures and heart defects are often related in dup19qter.
- Some features of these imbalances are not present in the present case, as sacral features associated to del7qter and clynodactyly associated to dup19qter.
- The presence of those two imbalances may complicate the final phenotype. Our patient is similar to other patients in other studies, presented with heteregenous phenotypic manifestations[2,22].
- Furthermore, in the present case, some features, as agenesis of central maxillary incisors, motor developmental delay, short stature and intellectual disability are not possible to confirm and quantify due to the newborn state of the proband.
- The important matter will be the counseling of the couple and to prevent future imbalances in their offspring.

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