International Journal of Genetics and Genomics
2024, Vol. 12, No. 4, pp. 81-85
https://doi.org/10.11648/j.ijgg.20241204.12

Case Report

Rare Maternal Structural Mosaicism as a Familial Cause of 18p Deletion Syndrome: Cytogenetics Mechanisms and Phenotypic Variability

Ana Clara Fandinho Montes[1], Ingrid Bendas Feres Lima[2], Thais Siqueira Fernandes[1], Carlos Roberto da Fonseca[2], Patr ćia Santana Correia[1], Cecilia Vianna de Andrade[4], Juan Clinton Llerena Junior[1, 3], Elenice Ferreira Bastos[2, *]

[1]Medical Genetic Center, Fernandes Figueira Institute, Oswaldo Cruz Foundation (IFF/FIOCRUZ), Rio de Janeiro, Brazil

[2]Clinical Cytogenetics Laboratory, Fernandes Figueira Institute, Oswaldo Cruz Foundation (IFF/FIOCRUZ), Rio de Janeiro, Brazil

[3]Medical School of Petropolis– University Center Arthur Sa Earp (UNIFASE), Petropolis, Brazil

[4]Anatomopathology and Cytopathology Coordination, Fernandes Figueira Institute, Oswaldo Cruz Foundation (IFF/FIOCRUZ), Rio de Janeiro, Brazil

Abstract

The chromosome 18p deletion (18p-) syndrome or monosomy of 18p is a rare chromosome abnormality, considered a contiguous gene deletion syndrome resulting from the deletion of a portion or most of the whole short arm of chromosome 18. Therefore, it can present a spectrum of phenotypes associated with different prognostic outcomes. Understanding the clinical variability of this condition is important once the fertility is preserved, impacting genetic counseling and reproductive outcomes. The aim of this article is to report a case of familial 18p deletion syndrome and its striking phenotypic variability within the same family. A male stillborn presenting alobar holoprosencephaly and his mother who presented with a single central incisor came to our attention for genetic investigation. Karyotype analysis and Fluorescent In Situ Hybridization (FISH) from a cordocentesis blood sample of the male stillborn was performed. Parents' cytogenetic analyses were obtained through peripheral blood cultures. Chromosomes were analyzed after GTG banding. FISH technique was carried out on both the proband's and maternal samples using WCP18 (whole chromosome 18) specific probes, according to the manufacturer's protocols. The stillborn karyotype and FISH analysis revealed a deletion characterized by 46, XY del(18)(p11.1→pter).ish del(18)(p11.1→pter)(wcp18-). His mother showed the same deletion in 45% of the analyzed cells revealing a rare structural mosaicism. The striking phenotypic variability encountered in this family could be attributed to a genetic combination of the deleted segment in the proband; and the presence of a mosaic normal karyotype may very well attenuate the mother's phenotypic presentation. The origin of an abnormally structural chromosome in mosaic possibly originated from a post-zygotic cell division event during the embryonic development of the mother. The consequences on the family offsprings of such rare cytogenetic event impacts greatly the family genetic counseling

*Corresponding author: Elenice.bastos@fiocruz.br (Elenice Ferreira Bastos)

Received: 10 September 2024; **Accepted:** 4 October 2024; **Published:** 26 November 2024

Keywords

18p Deletion Syndrome, Holoprosencephaly, Mosaicism, Phenotypic Range

1. Introduction

The 18p deletion syndrome (18p-) is a genetic condition caused by a total or partial deletion of the short arm of chromosome 18 [1]. Therefore, it's classified as a contiguous gene deletion syndrome. The phenotype can vary among patients because of the different sizes and locations of breakpoints and the genes involved in those regions [2]. The detection of the deletion can be determined by performing a karyotype collecting cells from different types of tissues, such as: amniotic fluid, chorionic villi, cordocentesis or peripheral blood. The deletions occur mainly *de novo* (85%), and for that matter parent's karyotype is normal. Patients presenting monosomy of 18p are fertile, thus direct familial transmissions may be rare but possible [1, 3]. Ring chromosome 18, cryptic subtelomeric deletion and chromosomal imbalances in structural rearrangements are also possible and increase the overall recurrence risk impact in future pregnancies [4]. Further assays, like Fluorescent In Situ Hybridization (FISH) and chromosomal microarray (CMA) can be helpful to confirm the deletion size and the genes involved [2, 5].

The most common clinical findings in patients with 18p- syndrome comprehend short stature; intellectual disability; Central Nervous System malformation (CNS) (i.e. holoprosencephaly), dystonia; genitourinary dysplasia and facial features (i.e. dysplastic ears, dropped corners of the mouth; single central incisors, microcephaly, epicanthic folds, short neck, pterygium colli) [2, 5].

This syndrome was the first partial monosomy compatible with life reported. It's rare with an estimated incidence of 1: 50.000 live births, being more prevalent in females than males [3, 4]. In about 15% of the cases, patients present with brain or facial malformations leading to holoprosencephaly. Ruling out the cases with CNS involvement, the life expectancy does not seem notably reduced [5].

In this article we report a case of a stillborn male infant diagnosed prenatally with alobar holoprosencephaly carrying a deletion of most of the short arm of chromosome 18 inherited from his mother who carried an associated 46, XX normal mosaic karyotype, leading to a milder clinical phenotype. Familial transmissions due to structural chromosome abnormalities occur less frequently than compared with *"de novo"* deletions. The phenotypic spectrum of this syndrome is notable due to the size of breakpoints and possibility of germline and/or somatic mosaicism as observed in the mother's phenotype with just a single central incisor compared to the stillborn with alobar holoprosencephaly.

2. Materials and Methods

Cell Culture, G-band Karyotype Analysis

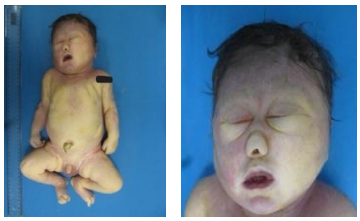
The cytogenetic study of the proband was carried out using a cordocentesis sample. The parents' karyotype was obtained from peripheral blood. Both types of samples were stimulated by phytohemagglutinin, analyzed after GTG banding (resolution level of 450 bands) and classified according to ISCN 2020 [6].

Fluorescence in situ hybridization analysis (FISH)

The FISH technique was carried out on both the proband's sample and the maternal sample, according to the manufacturer's protocols, using WCP18 (whole chromosome 18) specific probes (*Cytocell*, Inc.)

3. Case Report

Non-consanguineous parents with positive reproductive history for spontaneous misscarriage were referred to investigation in our center due to prenatal diagnosis of alobar holoprosencephaly (HPE) in a male fetus. A full-term stillborn male was born with multiple dysmorphims characterized by hypotelorism, bilateral proptosis and single nostril. (Figure 1) The propositus weight at birth was 3130 g, 49 cm of length and head circumference of 29 cm. Necropsy report revealed proboscis, agenesis of olfactory bulbs, extreme hypotelorism, wide and short neck, patent foramen ovale, bilateral adrenal hypoplasia and alobar holoprosencephaly with arhinencephaly. No other malformations were detected. The clinical examination of the mother revealed a normal head circumference and no dysmorphisms except for orthodontics correcting a single central incisor. The cytogenetic study of the stillborn identified a deletion of the short arm of chromosome 18 in all the metaphases evaluated (46, XY del(18)(p11.1→pter).ish del(18) (p11.1→pter) (wcp18-) (Figure 2). The father's karyotype was normal, while the mother had a mosaic karyotype characterized by the same deletion as the patient - mos 46, XX [11] /46, XX, del (18) (p11.1→pter) [9]. The maternal mosaicism was confirmed by FISH, which showed the 18p deletion in around 45% of the metaphases evaluated (Figure 3).



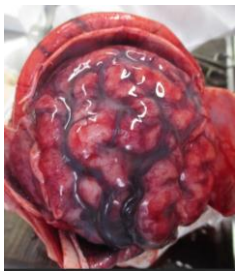


Figure 1. *Necropsy Gross findings: single nostril and hypotelorism. Brain necropsy: Alobar Holoprosencephaly.*

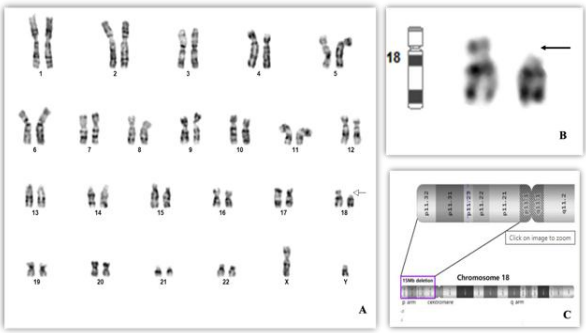


Figure 2. *A. The proband's karyotype revealed a 46, XY, del (18)(p11.2) complement in all 20 cells analyzed. B. Partial Karyotype of 18p deletion. C. Ideogram illustrating deleted 18p region.*

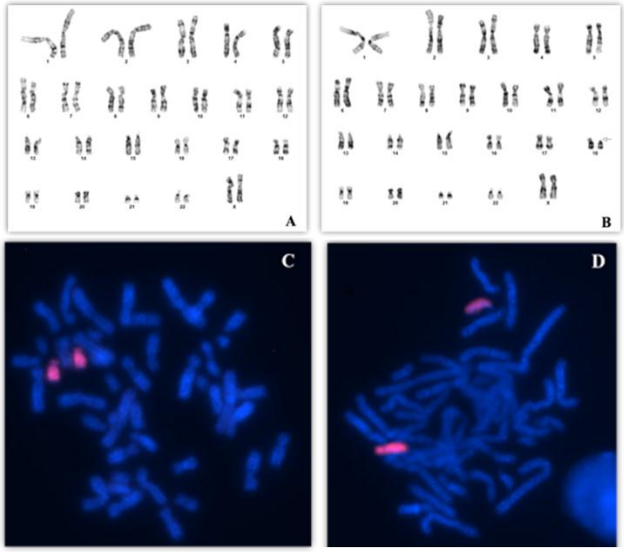


Figure 3. *A-B the mother's chromosomal analysis showed a mosaic pattern characterized by a 18p11.2 deletion in about 45% of analyzed metaphysis (46, XX, del 18p11.2-pter [9] and a 46, XX normal karyotype in 55% of cells [11]). C-D FISH analysis by WCP18 probe in mother's sample confirmed the deletion.*

4. Discussion

The 18p deletion syndrome or monosomy 18p is a chromosomal abnormality due to a deletion of most of the short arm of chromosome 18. Cases of unbalanced translocations and ring of chromosome 18 are possible causes [1, 4]. The incidence is roughly 1: 50,000 live-born infants [4].

Nearly 85% of the cases occur as a "*de novo*" event and therefore the proband's progenitor's karyotype is normal [1]. It is suspected that the remainder of cases occur due to imbalance structural rearrangements in parents' chromosomes [1, 3]. The unbalanced translocations usually involve the long arm of chromosome 18 with the long arm of some acrocentric chromosome [2].

In monosomy of 18p, the phenotype can be broad, including central nervous system impairment to short stature only. Different tissues can be affected carrying the deletion such as skin (i.e. hypopigmentation); eyes (i.e. strabismus; cataract); skeletal (i.e. kyphoscoliosis; clinodactyly; syndactyly; cubitus valgus; pectus excavatum); and others [7, 3].

Central nervous system impairment can manifest as hypotonia, microcephaly; malformations (i.e. holoprosencephaly) and intellectual disability. Speech delay, practical daily activities and behavior issues are present in some cases [7, 8]. The intelligence quotient (IQ) can vary between 25 and 75, nonetheless, most patients remain in 50 [5, 3]. There is evidence that the size and position of the deletion can be related with the severity of intellectual disability [7, 9]. In fact, as described by Koshy et.al (2010), the more distal and smaller the deletion, the more likely the cognition to be normal [9].

Holoprosencephaly and its microforms, such as central single incisor, are commonly found in patients with 18p deletion syndrome, affecting 10-15% of those. This can be explained by the location of the *TGIF* (transforming growth interacting factor) gene on the 18p11.3 region as the deletion of *TGIF* may be associated with holoprosencephaly [3]. Deletion of this gene is associated with an autosomal dominant pattern of inheritance with low penetrance, leading to phenotypic variability [10].

Prognosis can be poor in those who present with HPE [5]. Holoprosencephaly is a CNS malformation that occurs in the first three or four weeks of embryogenesis due to a disturbance in the prosencephalon cleavage. It can be classified as alobar (no segmentation with a large monoventricle); semi lobar (partial segmentation) and lobar (only the most rostral-inferior parts of the frontal lobe are fused) [11, 12]. There are several genetic and environmental conditions that can lead to HPE. The most common one is associated with trisomy 13; structural chromosomal abnormalities and some monogenic syndromes, such as Smith-Lemli-Opitz, have been reported as well [12].

Microforms of HPE include facial dysmorphism (hypotelorism), absence of olfactory bulbs and single central incisor, which can be associated or not to brain impairment. This minor form was reported as present in the proband ś mother [11, 12, 3].

As previously mentioned, 18p deletion syndrome displays a broad spectrum of phenotypes that can be explained by the size of the deletion, the genes involved and the presence of mosaicism [1].

Mosaicism is a postzygotic event in which two or more cellular lineages arise from a single zygote resulting in different genotypes. At the germline level, individuals can have two or more genotypes in their gametes, and it can be transmitted onto the offspring [13].

In our case, the stillborn was diagnosed with a deletion of the short arm of chromosome 18 in all the cells analyzed. In Chen, et.al (2013), they reported a case of a holoprosencephaly fetus with a distal 18p deletion (18p11.21-pter). Furthermore, their patient also presented with premaxillary agenesis and the deletion occurred *"de novo"*. In the present case, we report an 18p deletion comprising most of the short arm of chromosome 18 associated with a severe holoprosencephaly phenotype in the stillborn [10].

In Papamichail M, et.al (2024), a familial case of paternal balanced reciprocal translocation between the short arm of chromosome 8 and short arm of chromosome 18 was reported. In their study, the couple had a previous miscarriage due to holoprosencephaly and their third pregnancy was marked by a fetus presenting ventricular septal defect and micropenis. CMA technique was performed revealing a partial duplication of the short arm of chromosome 8 and a partial deletion of the short arm of chromosome 18 [14].

Although other familial cases of 18p deletion syndrome have already been reported as previously discussed, we report a familial case of 18p deletion syndrome and its striking phenotypic variation between the proband and his mother. While the fetus presented a very poor prenatal prognosis, leading to intrauterine death, his mother, on the other hand, who also presented the same deletion in 45% of the analyzed cells and a very mild phenotype, with only a single central incisor observed.

The deletion presented in this family possibly originated from a post-zygotic cell division event during embryonic development of the mother, an extremely rare event, and was transmitted to her son due to a possible germline mosaicism. Such event originates a great impact on family genetic counseling, since somatic mosaicisms together with sexual differences in gametogenesis may explain unexpected recurrences of genetic conditions, in general [15].

While searching for other cases reports in the literature, despite some being related to familial transmission of 18p deletion, none of them were correlated with maternal mosaicism. Thus, reinforcing the rarity of the presenting case.

5. Conclusions

18p- syndrome presents with a variable phenotype ranging from CNS developmental disorders such as intellectual disability to major congenital malformations such as holoprosencephaly. Mosaic karyotypes may attenuate phenotypic clinical presentation. This rare case of 18p- reinforces that structural chromosomal abnormalities should always be followed with karyotyping of the parents establishing assertive genetic counseling.

Abbreviations

FISH	Fluorescent in Situ Hybridization
CMA	Chromosomal Microarray
CNS	Central Nervous System
HPE	Holoprosencephaly
IQ	Intelligence Quotient

Author Contributions

Ana Clara Fandinho Montes: Investigation, Writing – original draft, Writing – review & editing

Ingrid Bendas Feres Lima: Formal Analysis, Investigation, Methodology, Writing – review & editing

Thais Siqueira Fernandes: Investigation, Writing – review & editing

Carlos Roberto da Fonseca: Methodology

Cecilia Vianna de Andrade: Formal Analysis, Methodology, Writing – review & editing

Juan Clinton Llerena Junior: Funding acquisition, Investigation, Project administration, Writing – review & editing

Elenice Ferreira Bastos: Formal Analysis, Investigation, Methodology, Supervision, Writing – review & editing

Conflicts of Interest

The authors declare no conflicts of interest.

References

[1] Goyal M, Jain M, Singhal S, Nandimath K. 18p deletion Syndrome: Case Report with Clinical consideration and Management. *Contemporary Clinical Dentistry*. 2017, 8 (4), 632-636. https://doi.org/10.4103/ccd.ccd_129_17

[2] Jin Q, Qiang R, Cai B, Wang X, Cai N, Zhen S, Zhai W. The Genotype Phenotype of Chromosome 18p Deletion Syndrome: Case Series. *Medicine (Baltimore)*. 2021, 100(8): e25777, 1-8. https://doi.org/10.1097/MD.0000000000025777

[3] Papamichail M, Eleftheriades A, Manolakos E, Papamichail A, Christopoulos P, Manegold-Brauer G, Eleftheriades M. Prenatal diagnosis of 18p deletion and 8p trisomy syndrome: literature review and report of a novel case. BMC Womens Health. 2024 Apr 15, 24(1): 241. https://doi.org/10.1186/s12905-024-03081-4

[4] Choi JY, Moon JU, Yoon DH, Yim J, Kim M, Jung MH. 18p Deletion Syndrome Originating from Rare Unbalanced Whole-Arm Translocation between Chromosomes 13 and 18: A Case Report and Literature Review. *Children (Basel)*, 2022, 9(7): 987, 1-7. https://doi.org/10.3390/children9070987

[5] Turleau C. Monosomy 18p. *Orphanet Journal of Rare*, 2008, 3(4), 1-5. https://doi.org/10.1186/1750-1172-3-4

[6] Jordan JM, Hastings RJ, Moore S. ISCN (2020): An International System for Human Cytogenomic Nomenclature. 2020. https://doi.org/10.1159/isbn.978-3-318-06867-2

[7] Jones K, Jones M, Campo M. 18p Deletion Syndrome. In *SMITH's- Recognizable Patterns of Human Malformation*. 7th edition. Elsevier; 2013, 62-63.

[8] Ju D, Zuo Z, Li X, Shi Y, Zhang Y, Xue F. Discovery of a Chinese familial deletion 18p syndrome due to a false positive result on noninvasive prenatal testing. Journal of Obstetrics and Gynaecology Research. 2021 February, 47 (2): 827-832. https://doi.org/10.111/jog.14565

[9] Koshy B, Mandal K, Srivastava VM, Loius PT, Danda S. Familial 18p deletion syndrome and 18p partial trisomy inherited from a mother with balanced translocation. *Clinical Dysmorphology*, 2011, 20(3), 148-151. https://doi.org/10.1097/MCD.0b013e328343b9b9

[10] Chen HP, Huang JP, Yung Y, et. Al. Chromosome 18p deletion syndrome presenting holoprosencephaly and premaxillary agenesis: Prenantal diagnosis and aCGH characterization using uncultured amniocytes. *Gene*, 2013, 527(2): 636-41. https://doi.org/10.1016/.j.gene.2013.06.081

[11] National Library of Medicine, "Holoprosencephaly Overview". Available from: [Acessed in 6 April 2024]

[12] Malta M, AlMutiri R, Martin CS, Srour M. Holoprosencephaly: Review of Embryology, Clinical Phenotypes, Etiology and Management. *Children (Basel)*, 2023, 10(4): 647. https://doi.org/10.3390/children10040647

[13] National Library of Medicine, "Genetics, Mosaicism". [Acessed in 6 April 2024]

[14] Papamichail M, Eleftheriades A, Manolakos E, Papamichail A, Christopoulos P, Manegold-Brauer G, Eleftheriades M. Prenatal diagnosis of 18p deletion and 8p trisomy syndrome: literature review and report of a novel case. BMC Womens Health. 2024 Apr 15, 24(1): 241. https://doi.org/10.1186/s12905-024-03081-4

[15] Ouwens KG, Jansen R, Tolhuis B, Slagboom P, Pennix BWJH, Boomsma DI. A Characterization of postzygotic mutations identified in monozygotic twins. *Human Mutation*, 2018, 39(10), 1393-1401. https://doi.org/10.1002/humu.23586