Submitted 10.21.10 | Revision Received 1.26.11 | Accepted 1.31.11

Deletion of 18p Syndrome

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DOI: 10.1309/LMAPLK2TVJBX5K9M

Abstract

The deletion of the short arm of chromosome 18 is considered to be 1 of the most frequently occurring chromosomal aberrations, causing a minimal abnormality visible at birth. It usually becomes more apparent after 3 years. The proband is a 15-year-old male who has had phenotypes manifested mainly by brachycephaly, broad faces, ptosis, downturned corners of the mouth, tooth abnormalities, broad neck with low posterior hairline, tunnel chest, hand abnormalities, mental retardation ranging from mild to severe, and other malformations. In addition, the chromosomal analysis for both parents showed normal karyotypes.

Phonotypical features were quite similar throughout other cases and in accordance with the usual phenotype of del (18p) suggested within the same cases and among the del (18p) cases described. The abnormality was clearer with a high resolution chromosomal study, which is the detection of subtle chromosome rearrangement that is only possible if the banding resolution is high enough to permit their visualization.

Keywords: genetics, AP pediatrics

The deletion of the short arm of chromosome 18 is now a well-known chromosomal aberration. It was first described by the French geneticist Jean de Grouchy in 1963.[1] Since then, more than 100 cases have been reported.[2]

The belief exists among geneticists that there are people with del (18p) who are so mildly affected that they might escape the diagnosis until their progeny has a severe del (18p) that is more severely affected. While this may be true, there is only 1 report in the literature to validate it.[3]

The phenotypic manifestations of this kind of deletion are very sparse at birth. The female to male ratio is 3:2, and birth weight averages 2600 g. The most frequent abnormalities consist of mild to moderate growth deficiency, mental retardation, microcephaly, ptosis, epicanthal folds, low nasal bridge, hypertelorism, large protruding ears, holoprosencephaly, and clinodactyly of the fifth finger (which was observed in about 10% and 20% of the cases, respectively). Mental retardation was mild to severe with an average intellectual quotient (IQ) between 45 and 50. Also, there was a significant discrepancy between verbal and non-verbal performance, with verbal performance being more severely affected.[2,9-10] Dystonias are also reported.[10]

There were several records in the literature of patients suffering from del (18p) who experienced a growth hormone deficiency.[4-7] A survey cohort of registered families who have children with del (18p) showed that 13 out of the 16 children whose parents returned the questionnaire were abnormally short. Several of the respondents had children who were therefore too young to have post-natal growth failure. Of those children, some were on growth hormone replacement therapy.

Of the 11 patients who had undergone growth hormone testing, 4 were not deficient. Therefore, from this small survey it appeared that a great majority of children with del (18p) were abnormally short, and of the short children tested for growth hormone deficiency, 64% were growth hormone deficient. Most of the children on the growth hormone replacement therapy were responding well to the treatment.

There are also several reports of individuals with del (18p) and dystonia, which is a movement disorder characterized by involuntary twisting or repetitive movement and abnormal postures.[8] The age of onset of this movement disorder was between 12 and 17 years of age.

Most cases of del (18p) were thought to originate from *de novo* deletions, which account for approximately 85% of cases.[11] The remainder is suspected to come from an unbalanced familial transmission of structural chromosomal rearrangements. Furthermore, new cytogenetic techniques have shown 1 case of an unbalanced subtelomeric translocation causing del (18p).[12]

On the other hand, the optimal chromosomal study for this sample preparation is a function of many factors, including the following: density culture initiation, optimal time of harvest, concentration and exposed duration to a mitotic arresting, and appropriate hypotonic treatment. These factors are essential for chromosomal spreading, which are essential to achieve good metaphase preparation. Long chromosome preparation was obtained through synchronization of the cell cycle or the use of various chromosome anti-contraction reagents. Moreover, other equally important factors are relative humidity, air flow, and ambient temperature during the slide-making process. The present study highlights the importance

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of achieving longer chromosome preparation with optimal banding qualities.

Case Report

The proband is a 15-year-old male who was born following a normal gestation and delivery without complications. The mother was 35 years old. The patient was referred to rule out fragile X syndrome by cytogenetics. The phenotypic manifestations were the following: brachycephaly, broad face, ptosis, downturned corners of the mouth, tooth abnormalities, broad neck with a low posterior hairline, tunnel chest, hand abnormalities, mental retardation with difficulties in memory skills and social rules, and other malformations.

Chromosomal analysis of heparinsed peripheral blood lymphocytes in sodium heparin was carried out using GTG banding in synchronized 72-hour cultures in complete RPMI 1640. One mL of whole blood was used to inoculate each 10 mL flask medium. Forty-eight hours after culture initiation, the blood culture was synchronized with 100 mL excess thymidine and returned to the incubator for another 24 hours. Following this, 100 mL of colcemid was added to the culture and incubated for an additional 15 minutes.

The procedure was performed on the proband's father and mother. The proband analysis revealed a 46, XX, del (18) (p11.2) complement in all 38 cells analyzed (**Image 1**).

Fragile X syndrome was ruled out by cytogenetics. The proband's mother and father revealed normal karyotype 46—XX karyotype for the mother and XY karyotype for the father.

Discussion

We present this case of a boy with an 18p deletion. Phenotypical features were quite similar throughout the other cases and in accordance with the usual phenotype of del (18p). Another feature consistent throughout the del (18p) cases was poor intellectual outcome. First, Uchida[15] described a child with a del (18p) who also had a developmental delay, performing at 65%-70% of normalcy. Furthermore, Velagaleti[14] presented a girl having an 18p11.2 with psychosocial evaluation that revealed a verbal IQ of 63 and a full scale IQ of 69, consistent with mild mental retardation. Another study by Tsukahara[15] showed a Japanese child also bearing del (18p11.2) with an IQ of 74 with significant speech delay, placing him on a borderline intellectual functioning level.

We would like to underscore the fact that among the cases presented above, chromosome 18p deletion was a rare chromosomal disorder in which all or part of the short arm (p) of chromosome 18 was deleted. The disorder is typically characterized by short stature, variable degrees of mental retardation, speech delays, malformations of the skull and facial (craniofacial) region, and/or additional physical abnormalities.

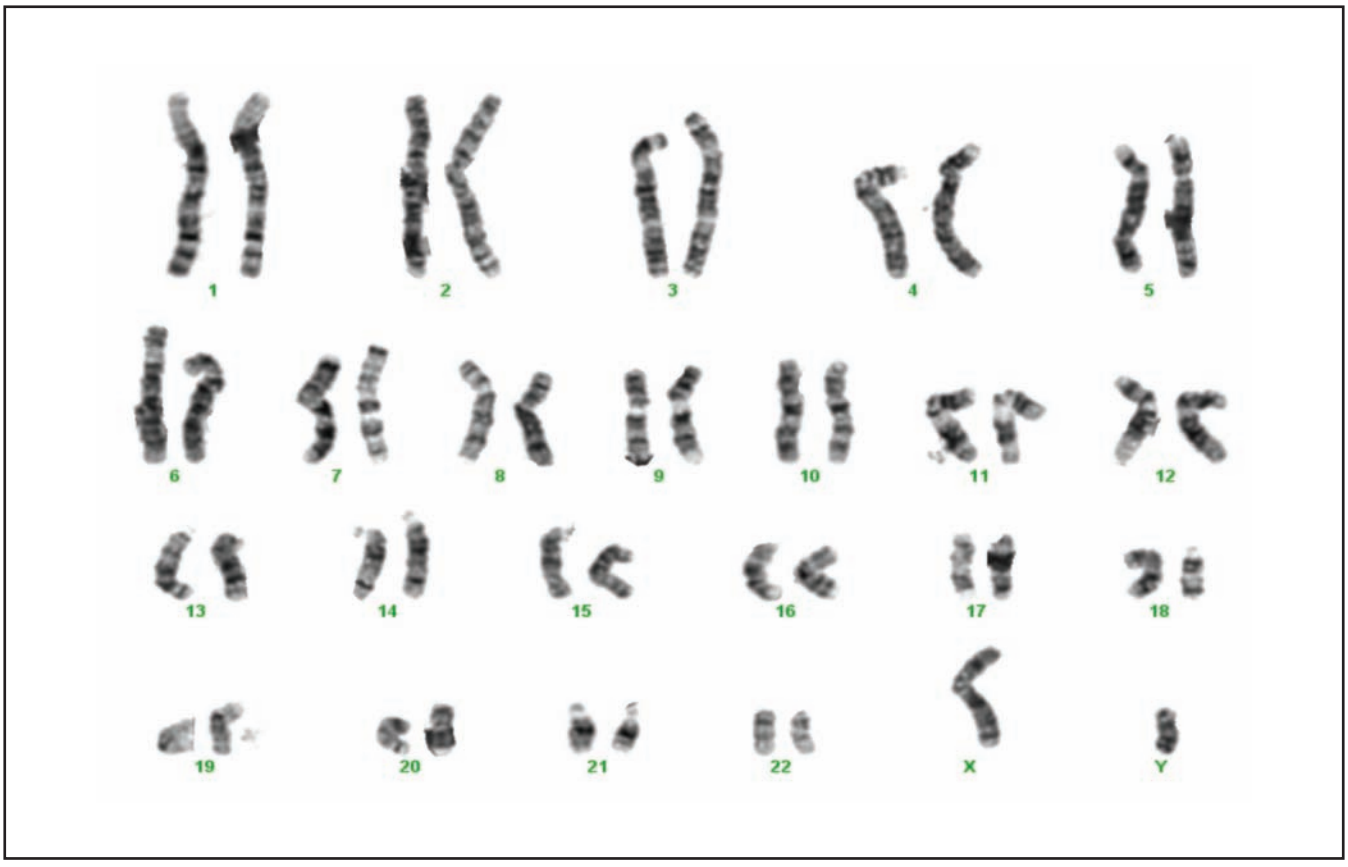

Image 1_G-banded karyotype showing the deletion of the short arm of chromosome 18 46, XY, 18p.

Associated craniofacial defects may vary greatly in range and severity from case to case. However, such features commonly include an unusually small head (microcephaly), a broad, flat nose, a "carp-shaped" mouth, large, protruding ears, widely-spaced eyes (ocular hypertelorism), and/or other abnormalities. Rarely (ie, in about 10% of cases), other neurologic findings and/or extremely variable midline facial defects, such as the presence of a single, central front tooth (maxillary incisor), closely spaced eyes (hypotelorism), an abnormal groove in the upper lip (cleft lip); incomplete closure of the roof of the mouth (cleft palate), and/or, in severe cases, absence of the nose and/or cyclopia. Cyclopia is characterized by fusion of the eye cavities (orbits) into a single cavity containing 1 eye. Research by Rigola[16] discussed the fact that none of the cases published had a history of spontaneous abortion.

On the other hand, we focused on the importance of the chromosomes' high resolution in picking up the del (18p) abnormality, in which chromosomes become progressively shortened as the cell progresses from interphase to metaphase. This behavior allows the chromatin to be neatly packaged for segregation into daughter cells at the end of telophase. As cell culture techniques evolve, cytogenetics analysis has gradually moved from being performed on mid-metaphase chromosomes to longer early metaphase or even late prophase chromosomes.

This can be accomplished (high-resolution chromosomal study) by synchronizing the cell cycle with a block at the S-phase and subsequent release with a releasing agent. Several block and release reagents are available, such as a methotrexate block with a thymidine release or an excess thymidine block with 2-deoxycytidine as a releasing agent.

In our laboratory, long chromosomes with high resolution are routinely gathered with a blood specimen. This is achieved by a combination of the cell synchronization and the addition of the chromosomes' anti-contraction additives. The protocols we employ comprise a 24-hour block with excess thymidine, but without an accompanying release period. This strategy does not block DNA synthesis completely, but instead, prolongs the S phase so chromosome condensation is reduced as the cells proceed toward metaphase. Detection of subtle chromosome rearrangement is possible only if the banding resolution is high enough to permit their visualization.

This report presents a case of del (18p) syndrome, in which the phenotypical features were similar throughout the other cases and in accordance with the usual phenotype of del (18p), suggested within the same cases and among the del (18p) cases described. Del (18p) is usually caused by spontaneous (*de novo*) errors very early in the development of the embryo that appear to occur randomly for unknown reasons.

Cytogenetics laboratories have a responsibility to attain and maintain a high standard of competency. This includes instituting methodology and technical protocols that will consistently yield long chromosome preparation so subtle rearrangements can pick up the del (18q) abnormality. These abnormalities may be missed with chromosome preparations that have a banding low resolution or with those preparations that have a poor morphology and suboptimal banding. LM

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