Journal of Genetic Syndromes & Gene Therapy
ISSN: 2157-7412

Akkuş et al., J Genet Syndr Gene Ther 2016, 7:2
DOI: 10.4172/2157-7412.1000287

Case Report Open Access

An Adult Patient with Monosomy 18p, Growth Hormone Deficiency and Selective IgA Deficiency

Pınar Zengin Akkuş[1]*, Arda Çetinkaya[2], Deniz Çağdaş Ayvaz[3], Mehmet Alikaşifoğlu[2], Ayfer Alikaşifoğlu[4], Nurgün Kandemir[4], İlhan Tezcan[3], Gülen Eda Utine[1] and Koray Boduroğlu[1]

[1]Hacettepe University, Ihsan Dogramacı Children's Hospital, Department of Pediatrics, Division of Pediatric Genetics, Ankara, Turkey
[2]Hacettepe University, Ihsan Dogramacı Children's Hospital, Department of Medical Genetics, Ankara, Turkey
[3]Hacettepe University, Ihsan Dogramacı Children's Hospital, Department of Pediatrics, Division of Pediatric Immunology, Ankara, Turkey
[4]Hacettepe University, Ihsan Dogramacı Children's Hospital, Department of Pediatrics, Division of Pediatric Endocrinology, Ankara, Turkey

Abstract

Monosomy 18p is a relatively frequent deletion syndrome with an estimated frequency of one in 50,000 liveborns. Most frequent findings consist of mild to moderate growth deficiency, intellectual disability, microcephaly, and facial dysmorphic features including ptosis, epicanthic folds, low nasal bridge, hypertelorism and large protruding ears. Anomalies of other systems may accompany. A 31-year-old male patient with dysmorphic facial features, congenital hypothyroidism, growth hormone deficiency and intellectual disability was diagnosed with monosomy 18p. The patient who also suffered from recurrent aphthous stomatitis and otitis during childhood and selective IgA deficiency was also diagnosed. Monosomy 18p in this patient was further analyzed with SNP microarrays. The 18p deletion caused monosomy of a segment larger than 18 Mb, which consisted many OMIM genes. Deleted genes in this region are known to have a diverse array of functions in various cellular processes. Estimating the possible pathogenic roles of these gene deletions over cellular functions may be difficult for today, however, precise delineation of molecular findings would lead to a better understanding of disease pathogenesis in future.

Keywords: 18p deletion syndrome; Growth hormone deficiency; Primary hypothyroidism; Selective IgA deficiency; SNP microarray

Introduction

Monosomy 18p was first described by de Grouchy and colleagues in 1963 [1] and since then, more than 150 cases have been reported [2]. Partial monosomy 18p is considered one of the most common deletion syndromes, with an estimated frequency of 1 in 50,000 live-born infants [3]. As the deletion may involve chromosome 18p partially or totally, the clinical phenotype varies widely. Mild to moderate growth deficiency, intellectual disability and facial dysmorphic features are usually present. The latter includes epicanthic folds, ptosis of the eyelids, low nasal bridge, hypertelorism, micrognathia, low set and large protruding ears, wide mouth with rounded face, and dental abnormalities [2]. The hands may be wide and short, and the neck may be short and webbed with a low posterior hair line [3]. Other anomalies may occasionally include cataracts, strabismus, genital anomalies, cardiac defects, syndactyly, fifth finger clinodactyly, dislocation of hips, talipes equinovarus, alopecia, hypopigmentation, and growth hormone deficiency [2]. Intellectual disability may be due to either central nervous system malformations, or 18p deletion syndrome itself. In 18p deletion, mild to severe intellectual disability may be present. IQ range from 25 to 75 with an average of approximately 45 to 50 [2]. Some of the patients have behavioral problems such as autism or schizophrenia accompanying the intellectual deficiency [3]. An association between IgA deficiency and chromosome 18 aberrations was first described by Feingold and his colleagues. [4] IgA levels lower than 10 mg/dl when other immunoglobulin levels are normal indicates selective IgA deficiency. This rarely accompanying feature has been previously reported both in 18p deletions, and also in 18q deletions [2,5,6] While reports of immunodeficiency with 18p deletion syndrome have mainly focused on selective IgA deficiency, some patients may have low levels of other immunoglubulins also [7]. A patient with monosomy 18p, diagnosed in adulthood, is herein presented with his clinical and molecular findings. The patient had various structural and developmental anomalies, as well as other systemic disorders. Rare combination of endocrinopathies with selective IgA deficiency, along with results of molecular genetic investigations is presented.

Case Report

The patient was admitted to genetics department for facial dysmorphic features and intellectual disability at the age of 31. He had been under medical follow-up for various systemic conditions since he was an infant. Past medical history revealed that he was the third child of a healthy non-consanguineous couple and he was born at term with a birth weight of 3600 gr by spontaneous vaginal delivery. Both parents and his two elder brothers were healthy and of average height. There was an early onset developmental delay, and all developmental milestones were late. He walked at 1.5 years, did not speak until 6 years of age, and he received special education for slow learners. Short stature was noted at 10 years of age, when his anthropometric measures were as follows; weight 18 kg, height 107 cm, and head circumference 50 cm (all below 3rd centile, and height SDS: -4.8). In laboratory evaluation, high levels of thyroid stimulating hormone (142 IU/ml with reference of 0.36-3.29 IU/ml) and low levels of thyroid hormones were detected. Thyroid scintigraphy showed small size of thyroid glands. He was diagnosed as congenital hypothyroidism and given thyroid hormone replacement therapy. By replacement therapy, thyroid hormone levels were held

***Corresponding author:** Pınar Zengin Akkuş, MD, Hacettepe University Faculty of Medicine, Department of Pediatrics, Department of Pediatric Genetics Ankara, Turkey, Tel: +90 312 311 55 22; Fax: +90 312 311 55 22; E-mail: pinarzenginakkus@gmail.com

Received November 23, 2015; **Accepted** February 15, 2016; **Published** February 22, 2016

Citation: Akkuş PZ, Çetinkaya A, Ayvaz DÇ, Alikaşifoğlu M, Alikaşifoğlu A, et al. (2016) An Adult Patient with Monosomy 18p, Growth Hormone Deficiency and Selective IgA Deficiency. J Genet Syndr Gene Ther 7: 287. doi:10.4172/2157-7412.1000287

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within normal limits. Magnetic resonance imaging of the brain was obtained for microcephaly and developmental delay, and this only showed pituitary gland hypoplasia. His IQ scores were recorded as 70-79, indicating borderline intellectual disability. His growth rate was low during the following years. At the age of 12, his bone age and height age were consistent with 6 years, but progressed in parallel below the lowest percentile. When he was evaluated for growth hormone deficiency, somatomedin-C and IGFBP3 levels were 33 ng/ml (70–479 ng/ml) and 1.55 µg/ml (1.6-4.5 µg/ml), respectively. Growth hormone provocation tests (L-Dopa and insulin tolerance test) were performed, the peak growth hormone responses being 6.7 ng/ml and 1.5 ng/ml, respectively (> 10 ng/ml). He was started on growth hormone replacement therapy at the age of 15, when his height was 122 cm. At the age of 19.5, when his bone age was 16 years and height was 158.7 cm, growth hormone therapy was ceased. Percentiles of height and weight for ages are shown in Graph 1. At the age of 17, he was referred to the outpatient clinics of pediatric immunology department for evaluation of recurrent aphthous stomatitis and otitis. Detailed immunological findings of the patient are presented in Table 1. Based on the immunoglobulin levels, the patient was diagnosed with selective IgA deficiency. On physical examination at genetics department at the age of 31, his height, weight and head circumference were 159 cm (below 3rd centile), 64 kg (below 3rd centile) and 55 cm (50th centile), respectively. Besides short stature, he had dysmorphic facial characteristics including flat nasal bridge, epicanthic folds, bilateral ptosis more evident in the right side, proptosis, full lips and short philtrum, as well as large prominent ears as shown in Figure 1. Auditory and visual examinations were normal. Karyotype analysis from peripheral blood lymphocytes revealed 46, XY, del (18) (p11.1) (Figure 2). This was first confirmed by fluorescence in situ hybridization (FISH) using Vysis® ToTelVysion 18p probe, and the karyotype was designated then as 46, XY.ish del (18) (p11.1p11.1) (D18S552-). An unbalanced segregation of parental balanced translocation of chromosomes, leading to monosomy 18p in the proband was suspected. However, only maternal blood sample was available for karyotype analysis, which revealed 46, XX. This cytogenetic change was further evaluated by genome-wide SNP genotyping, using Affymetrix® CytoScanTM HD platform, following manufacturer's instructions. Molecular karyotype thus obtained read: arr [hg19] 18p11.32q11.1 (136,226-18,521,285)x1. For other CNVs detected in this experiment, database analyses revealed absence of OMIM genes, except in the deleted region at 18p. None of the other CNVs was considered pathogenic in DECIPHER. Microarray analysis revealed size of monosomy 18p as 18,385 Kb. This deletion involved genes (with MIM numbers) USP14 (607274), THOC1 (606930), COLEC12 (607621), CETN1 (603187), TYMS (188350), ENOSF1 (607427), YES1 (164880), ADCYAP1 (102980), NDC80 (607272), SMCHD1 (614982), EMILIN2 (608928), LPIN2 (605519), MYOM1

	Value	Normal range
Complete Blood Count		
Hb (g/dl)	11	11.7-15.5
WBC (/mm³)	10100	4100-11200
Plt (/mm³)	220000	159000-388000
ALC (/mm³)	6600	1200-3600
ANC (/mm³)	2400	1800-6400
AEC (/mm³)	800	100-500
Immunoglobulins		
Ig A (mg/dl)	< 6.67	96-465
Ig G (mg/dl)	1220	907-1958
Ig M (mg/dl)	163	80-282
Anti A / Anti B	1/64 (+)	
Anti Hbs (IV)	59	Negative 0-10
Specific antibody (Pneumococcal polysaccharide vaccine response)	Low	
Lymphocyte subsets		
CD3 (%)	58.8	55-83
CD4 (%)	35	28-37
CD8 (%)	20.9	Oct-39
CD19 (%)	8.8	19-Jun
CD16 + 56 (%)	29.2	31-Jul
Lymphocyte transformation (Cpw)	Patient	Healthy Control
SI (PHA)	193830/3515	189568/3327
SI (Con A)	217371/3515	114757/3327
SI (PMA+Ion)	52333/3515	191080/3327
SI (AntiCD3)	159922/3515	56436/3327
NT, Not Tested; ALC, Absolute Lymphocyte Count; ANC, Absolute Neutrophil Count; AEC, Absolute Eosinophil Count		

Table 1: Immunologic findings of the present patient.

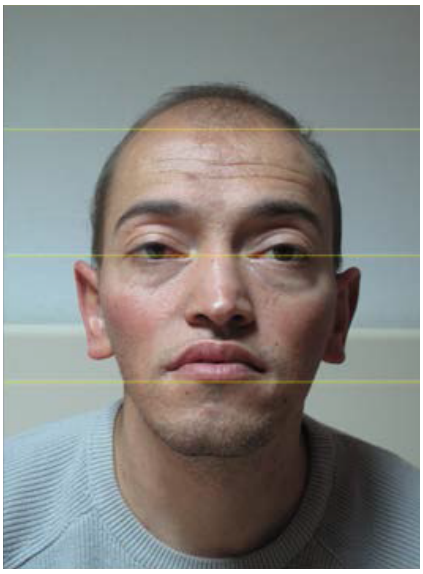


Figure 1: Dysmorphic facial features of the patient.

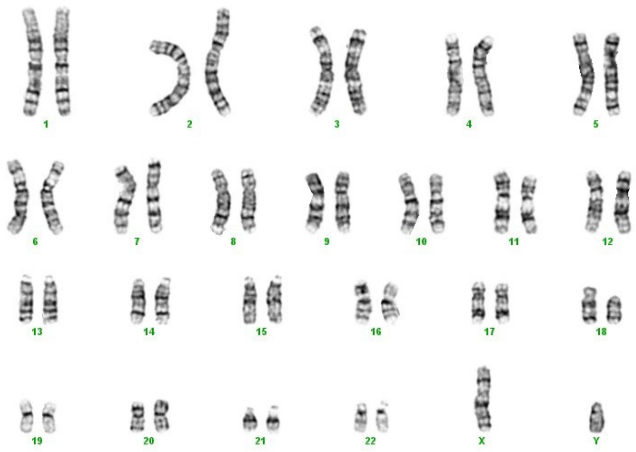
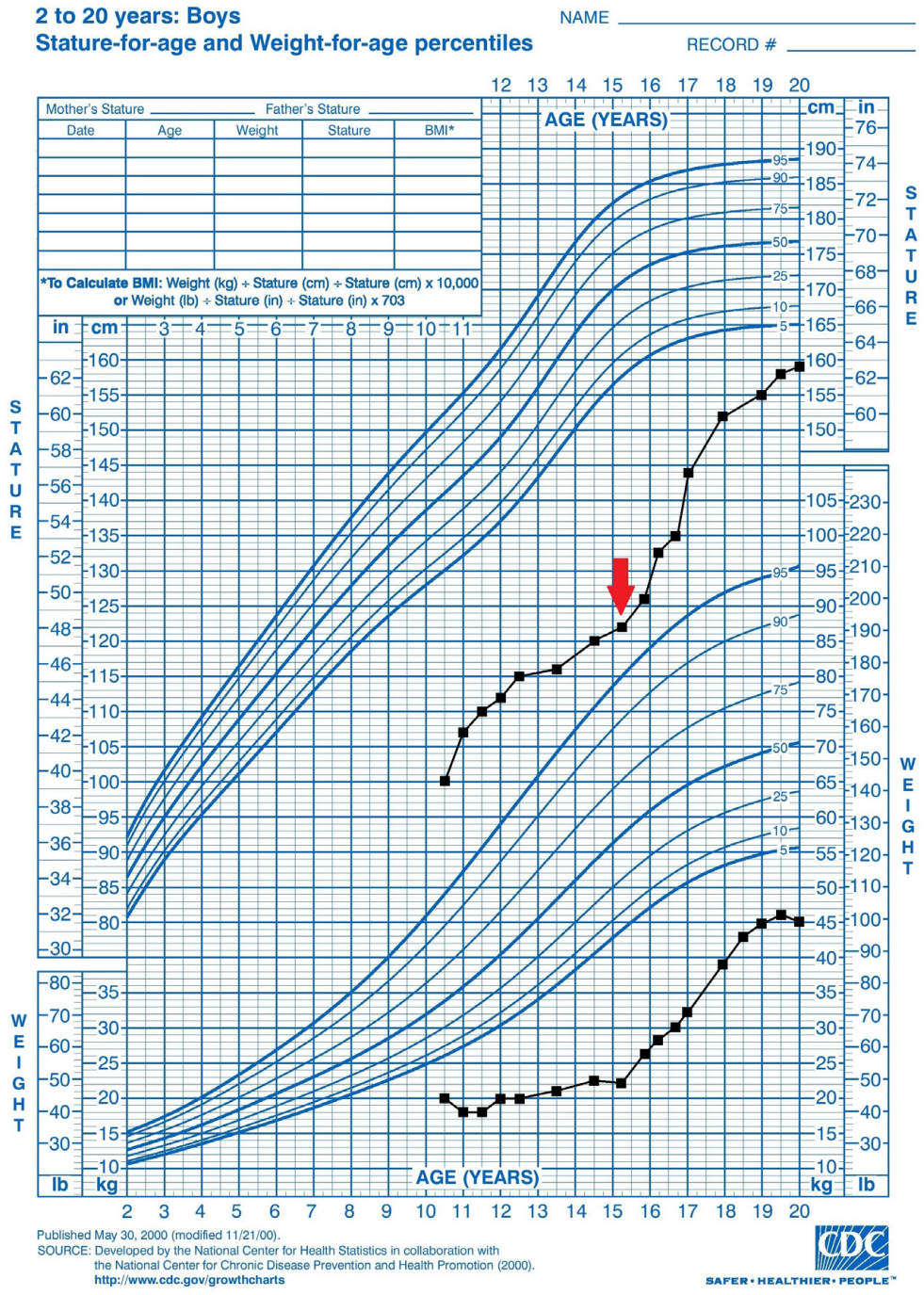


Figure 2: Karyotype analysis of the patient revealed 46, XY, del (18)(p11.1).



Graph 1: Percentiles of height and weight for age (Red arrow indicates the beginning of growth hormone replacement therapy).

(603508), MYL12B (609211), TGIF1 (602630), DLGAP1 (605445), ZBTB14 (602126), EPB41L3 (605331), ARHGAP28 (610592), LAMA1 (150320), PTPRM (176888), NDUFV2 (600532), ANKRD12 (610616), TWSG1 (605049), RALBP1 (605801), PPP4R1 (604908), RAB31 (605694), VAPA (605703), APCDD1 (607479), NAPG (603216), PIEZO2 (613629), GNAL (139312), CHMP1B (606486), MPPE1 (611900), IMPA2 (605922), CIDEA (604440), TUBB6 (615103), AFG3L2 (604581), SPIRE1 (609216), PSMG2 (609702), PTPN2 (176887), SEH1L (609263), LDLRAD4 (606571), RNMT (603514), MC5R (600042), MC2R (607397).

Discussion

On the basis of the clinical presentation and the results of genetic laboratory tools, 18p deletion was documented in the present patient. This deletion clinically consists of growth retardation, intellectual disability, dysmorphic features and systemic anomalies. Less frequent is immunoglobulin deficiency in this condition, and since selective IgA deficiency may be clinically silent, it should be investigated in patients with monosomy 18p. Phenotypical features in the patient including short stature, intellectual disability and dysmorphic facial

characteristics were consistent with the previously described phenotype of 18p deletion. In monosomy 18p, patients with short stature frequently have growth hormone deficiency and growth hormone supplementation, as was demonstrated in the present patient [8]. Borderline intellectual disability, with IQ scores 70-79, was also typical and congenital hypothyroidism might have expectedly contributed to the intellectual disability. However, our patient did not have any of the other structural anomalies of hands, eyes and teeth. The present patient was diagnosed with growth hormone deficiency and he had pituitary gland hypoplasia on cranial MRI. Besides he had a small thyroid gland suggesting primary hypothyroidism. Although it is interesting that the patient had isolated growth hormone deficiency and primary hypothyroidism, this presentation is suggestive for midline anomalies associating 18p deletions. However, no other midline structural defects have been detected in our patient. Deficiencies of immunoglobulins have been reported in chromosome 18 abnormalities, but only rarely. Recurrent infections may accompany due to specific antibody deficiencies associated with IgA deficiency. On the other hand, X-linked hypogammaglobulinemia with isolated growth hormone deficiency is a very rare condition [9]. Interestingly, autoimmune diseases such as thyroiditis, diabetes mellitus, rheumatoid arthritis or systemic lupus erythematosus may also accompany 18p deletion [6,10,11]. The present patient had endocrinopathies due to structural glandular anomalies, but not due to immune dysregulation. However, this report emphasizes the association of immunoglobulin A deficiency in monosomy 18p patients. Microarray analysis in our patient confirmed the deletion at 18p. This region consisted many known genes, as listed above with MIM numbers. These genes have a diverse spectrum of functions in various cellular processes, which will be evident by a search through databases. An OMIM search revealed that genotype-phenotype correlations, arising from heterozygous deletions of these genes, are difficult to establish in monosomy 18p for today. However, further delineation of genetic and cellular functions would later elucidate the pathogenic role of these deletions in monosomy 18p.About 2/3 of the cases of monosomy 18p syndrome are due to de novo deletions [12]. Many other cases result from unbalanced whole arm translocations, usually between the long arm of an acrocentric chromosome and the long arm of chromosome 18, resulting in a karyotype with 45 chromosomes [13]. In such a condition, parental karyotypes must be studied to detect a parent with a balanced translocation. Maternal karyotype revealed a normal constitution in the present case; however, paternal karyotype was unavailable. Deletion of 18p appears sometimes as a result of a ring chromosome, or after recombination in a pericentric inversion which may lead to 18p monosomy associated with 18q trisomy [14]. The recurrence risk for siblings is not significantly increased above that of the general population in those cases that arise de novo [3]. However, prenatal diagnosis by amniocentesis or chorionic villus sampling may be recommended, since cryptic germline mosaicism may be present in one of the apparently normal parents. In absence of severe malformations, survival does not seem to be reduced in the patients with 18p deletion [15]. For follow-up of patients suffering from 18p deletion, early rehabilitative and educational interventions, as well as physical therapy are recommended. All patients should be followed-up for growth retardation, immune deficiency or autoimmune disorders, as well as for other complications of the disease. Since monosomy 18p should be tested for it. Besides, careful evaluation of patients may perhaps reveal a pattern of midline defects in these patients.

Conclusion

Combination of unrelated abnormalities in a patient should raise suspicion of a chromosomal abnormality. Minor dysmorphic features with short stature, intellectual disability and hormone deficiencies, as well as selective IgA deficiency may suggest presence of an underlying monosomy 18p. Deleted genes in this region are known to have a diverse array of functions in various cellular processes. Estimating the possible pathogenic roles of these gene deletions over cellular functions may be difficult for today, however, precise delineation of molecular findings would lead to a better understanding of disease pathogenesis in future.

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