81957_Auto_Edited.docx

WORD COUNT 1926
TIME SUBMITTED 28-JAN-2023 05:11PM
PAPER ID 95990923

Name of Journal: *World Journal of Medical Genetics*
Manuscript NO: 81957
Manuscript Type: CASE REPORT

Phenotypic and cytogenetic features of an Iranian child with tetrasomy 18p syndrome: A case report

Sara Esmaeili, Cory J Xian

Abstract

BACKGROUND

Tetrasomy 18p is a rare chromosome abnormality disorder known to have considerable variability in clinical features and gathering data from different cases will help clinicians and researchers learn about its genotype-phenotype relationship and diagnosis.

CASE SUMMARY

Herein, we have reviewed the literature on phenotypic features of this disorder and described the phenotypic and cytogenetic features of a girl of early childhood with tetrasomy 18p for the first time from Iran. This patient showed a strong sense of smell (a unique feature not reported previously for this syndrome), had clenched hand, pes planus, forward head posture in walking and hirsutism (dysmorphic features less reported), and showed 10 clinical features that are generally observed in previously reported cases, including developmental delay/intellectual disability, triangular face, smooth philtrum, feeding difficulties, hypotonia, epicanthus, strabismus, history of constipation, growth retardation and foot anomalies. G-banding chromosome analysis from peripheral blood revealed an abnormal female karyotype with a small marker

chromosome (47,XX, +mar), and oligo-array comparative genomic hybridization displayed a gain of 14Mb of the 18p arm containing 56 OMIM genes in this patient. Overall, this patient seems to have mild phenotypes.

CONCLUSION

This Iranian tetrasomy 18p child displays a uniquely strong sense of smell, some less reported dysmorphic features and ten features generally reported.

Key Words: Tetrasomy 18p; Phenotypic features; Clinical features; Chromosome abnormality; Cytogenetic analysis; Case report

Esmaeili S, Xian CJ. Phenotypic and cytogenetic features of an Iranian child with tetrasomy 18p syndrome: A case report. *World J Med Genet* 2023; In press

Core Tip: Gathering data from different cases for the rare tetrasomy 18p chromosome abnormality disorder will facilitate mastering its genotype-phenotype relationship and diagnosis. This report described features for the first time for an Iranian patient. Compared to previously reported cases, this Iranian child displays a uniquely strong sense of smell, some less reported dysmorphic features and ten features generally reported. Her cytogenetic analyses revealed a small marker chromosome with a gain of 14Mb at the 18p arm. Apart from the usual clinical assessments, the non-invasive prenatal genetic testing is suggested to be used as a more accurate screening for detecting tetrasomy 18p.

INTRODUCTION

Tetrasomy 18p is a rare chromosome abnormality occurring in approximately 1 per 180000 Live births which affects both males and females equally. In tetrasomy 18p, there is an additional iso-chromosome which is composed of two copies of chromosome 18 short arm. Thus, each cell has four copies of the short arm[1-5]. Iso-chromosome 18p is

one of the most frequent iso-chromosomes in humans[3,6]. It has been suggested that maternal meiosis II nondisjunction followed by meiotic misdivision at the centromere is responsible for tetrasomy 18p. Thus, the maternal age can play a role in the formation of the iso-chromosome 18p[1,7,8].

While the clinical features of the tetrasomy 18p are variable, the main features of patients with tetrasomy 18p are growth retardation, neonatal jaundice, microcephaly, seizures, strabismus, heart defects, abnormalities in muscle tone, a history of constipation and gastroesophageal reflux, and scoliosis/kyphosis[9-15]. Because of phenotypic feature variability, gathering data from different cases will help clinicians and researchers learn about genotype-phenotype relations and diagnosis of tetrasomy 18p[16,17].

In this paper, we have reviewed the literature on phenotypic features of this disorder with the cases indexed in PubMed with the search term of "Tetrasomy 18p", and we have described the phenotypic and cytogenetic features of a girl of early childhood with tetrasomy 18p for the first time from Iran.

CASE PRESENTATION

Chief complaints

A girl of early childhood was referred for genetic analysis due to intellectual disability, hypotonia, speech delay, strabismus, valgus deformity or feet anomaly (Figure 1A) together with pes planus (Figure 1B). The girl showed developmental delay in her infancy at which time she could not sit, made no speech-like sound, and paid no attention to surroundings.

History of present illness

Triangular face, epicanthus and smooth philtrum are other dysmorphic features of the patient. At early childhood, evidence of strabismus can still be seen on her face (Figure 1C) although it had been partially treated by surgery at 9-months' age. Other

dysmorphic features found included mild hirsutism (Figure 1D), clenched hands (Figure 1E) and forward head posture in walking.

History of past illness

At infancy, she presented with difficult breastfeeding and severe cries, she had epilepsy-like symptoms, and she developed strabismus.

Personal and family history

The patient's parents were healthy and non-consanguineous. At the time of trying to conceive, the mother was receiving antibiotic treatment for Listeriosis. At the end of the pregnancy and prior to giving birth to the baby girl, the mother had bed rest at home for one month for preventing premature birth and preterm labor. The ultrasound scans during pregnancy and screening evaluations were normal. At the time of patient's birth, the mother and the father were 30 and 29, respectively. The infant was born at 38 wk of gestation by cesarean section, weighing 3000 g with a length of 48 cm and head circumstance of 32.5 cm.

Physical examination

Using Gilliam Autism Rating Scale (GRAS)[18] and through parental report, the probability of autism was evaluated in the patient, and her score of 38 indicated a low probability of autism. The results of her echo-cardiography evaluations were also normal.

Laboratory examinations

Peripheral blood specimens from the patient and her parents were collected for cytogenetic analyses. Twenty metaphase spreads from cultured blood lymphocytes were analyzed using G-banding technique at the resolution of 400 bands. Chromosome analysis in the patient revealed the abnormal female karyotype with a small marker chromosome (47,XX, +mar) (Figure 1F), while karyotypes of her parents were normal.

Imaging examinations

Although she had epilepsy-like symptoms at infancy, her brain ultrasonography and brain magnetic resonance imaging (MRI) evaluations showed normal results.

Further diagnostic work-up

Further investigation for copy number changes by Oligo-Array Comparative Genomic Hybridization (CGH) showed the gain of 13.9 Mb on 18p11.32p11.21 from nucleotide 148963 to 14081887 (Figure 1G). The pathogenic region was assessed and revealed that it contains 56 OMIM genes. These results are compatible with tetrasomy of 18p.

FINAL DIAGNOSIS

With the patient's medical history and combined with clinical and cytogenetic features, the final diagnosis of this Iranian girl was tetrasomy of 18p disorder.

TREATMENT

Strabismus that developed at birth was treated partially with surgery at the age of 9 mo.

OUTCOME AND FOLLOW-UP

The patient currently still shows intellectual disability.

DISCUSSION

This is the first case report of a child with tetrasomy 18p from Iran. This genetic disorder shows variable clinical characteristics. Among the 31 most reported features from tetrasomy 18p patients (listed in Table 1), our case had only 10 clinical features that are generally observed in most previously reported cases, including developmental delay/intellectual disability, triangular face, smooth philtrum, feeding difficulties, hypotonia, epicanthus, strabismus, history of constipation, growth retardation and foot anomalies. Dysmorphic features like clenched hand, pes planus, forward head posture

in walking and hirsutism observed in our case are less reported in tetrasomy 18p patients. Although features such as small mouth, low-set ears, microcephaly, brain MRI variants, scoliosis/kyphosis, recurrent otitis media, jaundice, cardiac defects, and epilepsy were not seen in our patient, they have been reported in at least 25% tetrasomy 18p cases (Table 1). However, our patient showed the unique feature – having a strong sense of smell, which was not reported as a common feature for this syndrome. Overall, this patient seems to have mild phenotypes.

In 2015, 43 children with tetrasomy 18p were assessed to determine the probability of autistic behaviors, and the results demonstrated that some individuals who had mild cognitive deficits did not show characteristics associated with autism[19]. In the present study, the result of GRAS showed that the girl did not exhibit behaviors like a child with autism. However, she was educable; for example, she has learned feeding ducks and played with familiar children.

Although it has been reported that the tetrasomy 18p occurs usually de novo, some studies reported both paternal and maternal origins[6,7,16,20,21]. In our case, the karyotypes of parents were normal; so, the abnormality of chromosome 18 was not inherited.

Array CGH displayed a gain of 14Mb of the 18p arm in this patient. Among genes located in this pathogenic region, some are associated to developmental disorder phenotypes according to OMIM database (https://www.omim.org/), including LAMA1, GNAL, TGIF1, PIEZO2, AFG3L2 and MC2R. Another gene in the duplicated region was SMCHD1, an epigenetic regulator which has recently been found to have functions during development and developmental disorders[22,23]. Interestingly, the existence of AFG3L2, MC2R, TGIF1, SMCHD1, LAMA1 and PIEZO2 genes in the duplicated region was reported previously in tetrasomy 18p cases[9,17]. Thus, the patient's developmental disorders such as delayed motor development, speech delay, psychomotor retardation and hypotonia might be related to these genes. In addition, although the SMCHD1 gene has been reported to have a role in the Bosma arhinia and micropthalmia disorder where the patients have problems with the sense of smelling

[22], further studies are required to establish whether and how the over-production of SMCHD1 gene or other genes in the duplicated region may contribute to the patient's phenomenon of having a very strong sense of smell.

As mentioned above, during pregnancy all screening evaluations, laboratory tests, and ultrasounds scans were normal, and no suspicious findings were found. Also, the birth weight, length and head circumstance were normal. Because of the disease rarity and variety of clinical features in tetrasomy 18p, the prenatal diagnosis of this abnormality is difficult [7]. It has been demonstrated that the non-invasive prenatal testing (NIPT) can be used to detect tetrasomy 18p using cell-free DNA screening technology without any procedural risk of miscarriage[3,24,25]. Therefore, it is suggested that in addition to the usual assessments during pregnancy, NIPT can be used as a more accurate screening test to detect tetrasomy 18p during pregnancy and prior to the birth of an abnormal baby.

CONCLUSION

To the best of our knowledge, this is the first case report of a child with tetrasomy 18p from Iran. In this study, we have reviewed the literature reported in PubMed on phenotypic features of this rare chromosome abnormality disorder and described the phenotypic and cytogenetic features of this Iranian girl of early childhood with tetrasomy 18p. This patient showed 10 clinical features that are generally observed in most previously reported cases, and she had dysmorphic features including clenched hand, pes planus, forward head posture in walking and hirsutism that are less reported in tetrasomy 18p patients. Furthermore, this patient showed the unique feature of having a strong sense of smell, which was not reported for this syndrome. G-banding chromosome analysis revealed an abnormal female karyotype with a small marker chromosome (47,XX, +mar) with karyotypes of her parents being normal, and oligo-array comparative genomic hybridization displayed a gain of 14Mb containing 56 OMIM genes of the 18p arm in this patient. Overall, while this patient seems to have mild phenotypes, further genetic work is required to define its underlying genetic

defect for the unique feature of having a strong sense of smell. Based on assessments for this case and the literature, it is suggested that in addition to the usual clinical assessments during pregnancy, the non-invasive prenatal genetic testing can be used as a more accurate screening test to detect tetrasomy 18p prior to the birth of an abnormal baby.

ACKNOWLEDGEMENTS

We would like to thank the patient and her parents for their cooperation and support.

81957_Auto_Edited.docx

ORIGINALITY REPORT

1 %

SIMILARITY INDEX

PRIMARY SOURCES

1	Alvaro Moreira, Hrishikesh Das, Minire Hasi-Zogaj, Bridgette Soileau et al. "Abnormal bone mineral content and density in people with tetrasomy 18p", American Journal of Medical Genetics Part A, 2019 Crossref	25 words — 1%

EXCLUDE QUOTES	ON	EXCLUDE SOURCES	< 12 WORDS
EXCLUDE BIBLIOGRAPHY	ON	EXCLUDE MATCHES	< 12 WORDS