International Journal of Contemporary Pediatrics
Pande S et al. Int J Contemp Pediatr. 2017 Jul;4(4):1545-1548
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: http://dx.doi.org/10.18203/2349-3291.ijcp20172706

Case Report

Immunodeficiency, centromeric heterochromatin instability of chromosomes 1, 9, and 16, and facial anomalies: the ICF syndrome

Shailesh Pande[1]*, Mani Bhushan[2], Anurita Pais[1], Gauri Pradhan[1], Chaitali Kadam[1], Sunmeet Matkar[1]

[1]Department of Cytogenetics, Metropolis Healthcare Limited, Kurla (W), Mumbai, Maharashtra, India
[2]Department of Pediatrics, Advanced child care and cure, Haniman Nagar, Kankarbagh, Patna, Bihar, India

Received: 01 March 2017
Accepted: 28 April 2017

***Correspondence:**
Dr. Shailesh Pande,
E-mail: shailesh.pande@metropolisindia.com

ABSTRACT

Instability of the heterochromatic centromeric regions of chromosomes 1 associated with immunodeficiency was found in a 3 and half months old girl. The case was referred to Department of Genetics, Global Reference Laboratory, Metropolis Healthcare Ltd, Mumbai with the suspicion of Downs Syndrome for chromosomal karyotyping. This patient had facial anomalies in addition to combined immunodeficiency and chromosomal instability. Stretching of the heterochromatic centromeric regions of chromosomes 1 and homologous and non-homologous associations of these regions were the most common cytogenetic findings in this patient. Multi-branched configurations and whole arm deletions of chromosomes 1 were also found. Comparing clinical and chromosomal data we conclude that the patient was suffering from immunodeficiency, centromeric heterochromatin instability and facial syndrome. The chromosomal karyotyping report was showing instability around vicinity of chromosome 1 and various abnormalities around vicinity of both chromosomes 1 were found in form of random breakages of chromosome 1, fragile sites, deletions/duplications of small and long arm, extra copies of chromosome 1 with rosette formations, exchange of arms and partial aneuploidies of chromosome 1. Further, the investigations regarding the immune status revealed that the level of IgM (5.98 mg/dl), IgA (<6.16mg/dl) and IgG (92.10 mg/dl) subgroup of immunoglobulin was very low. The results were consistent with The Immunodeficiency, Centromeric region instability, Facial anomalies (ICF) syndrome. Second sample from the patient for molecular studies could not be collected and performed since the patient failed to survive after 3 and half months.

Keywords: Immunoglobulin, Immunodeficiency centromeric region instability facial anomalies syndrome, India, Karyotyping

INTRODUCTION

The Immunodeficiency, Centromeric region instability, Facial anomalies syndrome (ICF) is a rare autosomal recessive condition.

Patients with this condition shows immunodeficiency, although B cells are present, and by specific cytogentic findings in the vicinity of the centromeres (the juxtacentromeric heterochromatin) of chromosomes 1 and 16 and sometimes 9.

The clinical findings of this syndrome are usually mild facial dysmorphism, growth retardation, failure to thrive, and psychomotor retardation.

CASE REPORT

The proband was a three and half month female baby born to a non consanguious marriage by lower (uterine) segment Caesarean section (LSCS) with suspicion of Down's syndrome. The blood sample for chromosomal karyotyping was send to Department of Genetics, Global Reference Laboratory, Metropolis Healthcare Ltd, Mumbai The chromosomal karyotyping report was showing instability around vicinity of chromosome 1 and various abnormalities around vicinity of both chromosome 1 were found in form of random breakages of chromosome 1 in the form of fragile sites, deletions/duplications of small and long arm, extra copies of chromosome 1 with rosette formations, exchange of arms and partial aneuploidies of chromosome 1. Further the case was discussed with referring doctor and further investigation for immune status of the baby was discussed. The investigations regarding the immune status revealed that the level of IgM (5.98 mg/dl), IgA (<6.16mg/dl) and IgG (92.10 mg/dl) subgroup of immunoglobulin was very low. Most patients with ICF syndrome die of infection at a young age, usually in the first or second decade of life. The patient had a flat nasal bridge, Mongolian slant of eyes, hypertelorism and slight low set ears. Some dysmorphism of face was noticed.

Table 1: Type of chromosomal aberrations.

Chromosomal abnormality	No. of cells
Centromeric region breaks and deletions	12
Centromeric region decondensation	54
Multibranched chromosomes	34

Table 2: Serum immunoglobulin profile (IgG, IgM and IgA).

Immunoglobulin	Observed value (mg/dl)	Biological reference interval
IgG total	92.10	400
IgM total	<6.160	1-91
IgA total	5.98	34-206

DISCUSSION

The Immunodeficiency, Centromeric region instability, Facial anomalies syndrome (ICF) is a rare autosomal recessive disease. It is characterized by immunodeficiency, although B cells are present, and by characteristic rearrangements in the vicinity of the centromeres (the juxtacentromeric heterochromatin) of chromosomes 1 and 16 and sometimes 9.[1] Other variable symptoms of this probably under-diagnosed syndrome include mild facial dysmorphism, growth retardation, failure to thrive, and psychomotor retardation.[2] Serum levels of IgG, IgM, IgE, and/or IgA are low, although the type of immunoglobulin deficiency is variable.[1]Recurrent infections are the presenting symptom, usually in early childhood.[3] ICF always involves limited hypomethylation of DNA and often arises from mutations in one of the DNA methyltransferase genes (DNMT3B).[4]

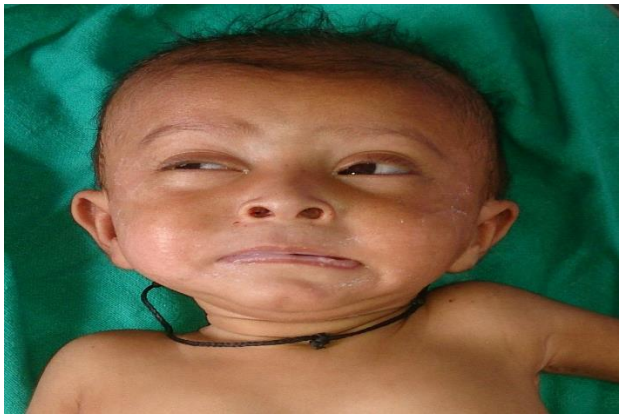

Figure 1: Case study of three and half month female baby.

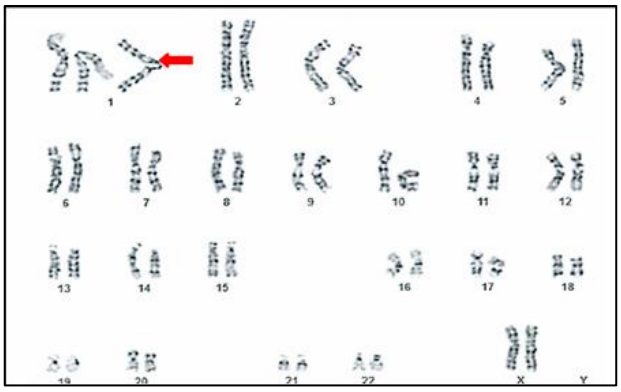

Figure 2: Tetrasomy of long arm of chromosome 1 (as shown by red arrow).

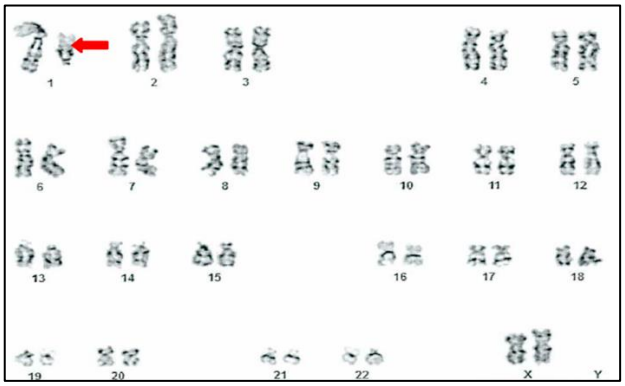

Figure 3: Deletion of long arm of chromosome 1(as shown by red arrow).

Much of this DNA hypomethylation is in 1qh, 9qh, and 16qh, regions that are the site of whole-arm deletions, chromatid and chromosome breaks, stretching (decondensation), and multiradial chromosome junctions in mitogen-stimulated lymphocytes. By an unknown mechanism, the DNMT3B deficiency that causes ICF

interferes with lymphogenesis (at a step after class switching) or lymphocyte activation. With the identification of DNMT3B as the affected gene in a majority of ICF patients, prenatal diagnosis of ICF is possible.

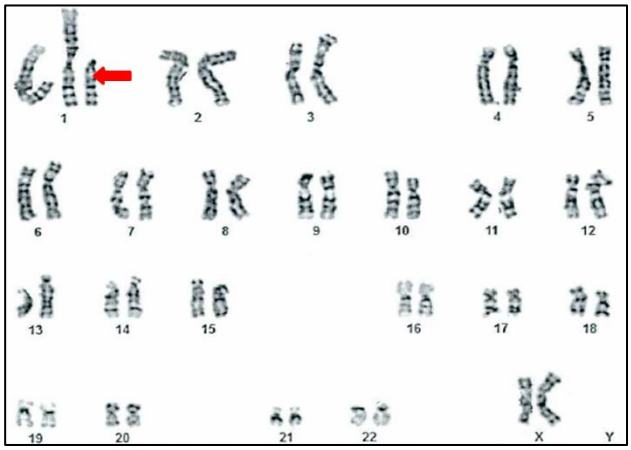

Figure 4: Trisomy of long arm of chromosome 1 (as shown by red arrow).

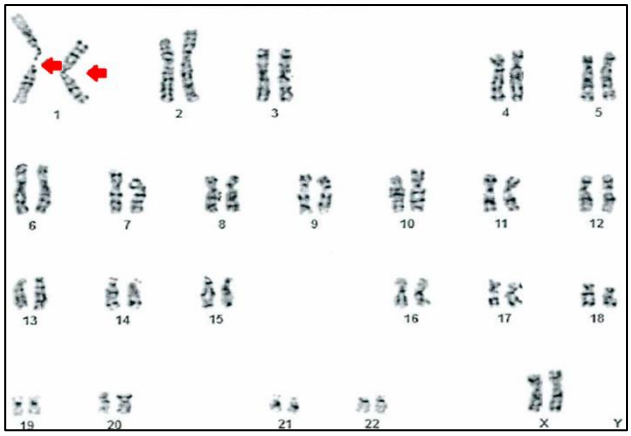

Figure 5: Exchange of arms in chromosome 1 (as shown by two red arrows).

However, given the variety of DNMT3B mutations, a first-degree affected relative should first have both alleles of this gene sequenced. Treatment almost always includes regular infusions of immunoglobulins, mostly intravenously. Recently, bone marrow transplantation has been tried. ICF is diagnosed by standard metaphase chromosome analysis of peripheral blood from paediatric patients (often babies or toddlers) displaying otherwise unexplained recurrent infections, which are usually severe pulmonary or gastrointestinal infections, despite the presence of B cells.[5]

Metaphases from phytohemagglutinin-stimulated blood cultures exhibit the following anomalies: whole-arm deletions and pericentromeric breaks of chromosomes 1 and 16 and sometimes 9; multi-branched chromosomes containing three or more arms of chromosomes 1 and 16 joined in the vicinity of the centromere (mostly at the 1qh or 16qh region); and occasional isochromosomes and translocations with breaks in the vicinity of the centromere.

In addition, prominent stretching (decondensation) in the 1qh and 16qh region is seen in chromosomes 1 and 16. Stimulation of ICF blood cultures with pokeweed mitogen produces similar anomalies. In most, but not all patients, chromosome 1 is affected more frequently than chromosome 16.[6]

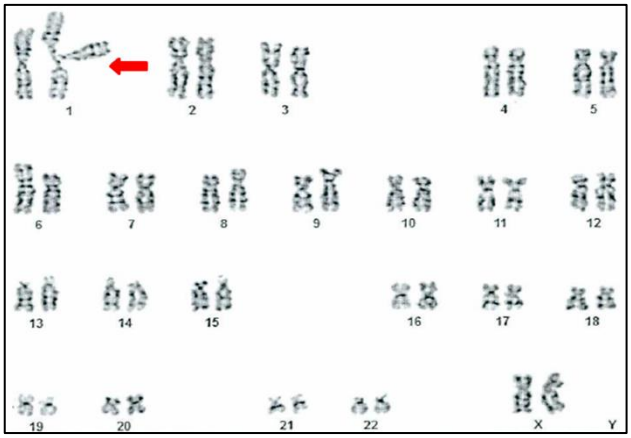

Figure 6: Random breaks and reunion at fragile site of chromosome 1 (as shown by red arrow).

Although many patients have low in vitro stimulation indices for either phyto-hemagglutinin or pokeweed mitogen, this is not an invariant finding and sufficient metaphases accumulate for cytogenetic analysis. Standard metaphase analysis after incubation of blood with mitogen for 72 or 92 hours allows the development of maximal frequencies of the ICF-associated chromosomal rearrangements.

Figure 7: Multiple copies of chromosome 1 with rosette formation (as shown by red arrow).

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Ehrlich M, Jackson K and Weemaes C. Immunodeficiency, centromeric region instability, facial anomalies syndrome (ICF). Orphanet J Rare Dis. 2006;1(2):1-9.
2. Hagleitner MM. Clinical spectrum of immunodeficiency, centromeric instability and facial dysmorphism (ICF syndrome). Journal of Medical Genetics. 2008;45:93-9.
3. Sathasivam S, Selvakumaran A, Jones QC, and Wathen CG. Immunodeficiency, centromeric region instability and facial anomalies (ICF) syndrome diagnosed in an adult who is now a long-term survivor. BMJ Case Reports. 2013 bcr2013200170.
4. Ehrlich M. ICF, an Immunodeficiency Syndrome: DNA Methyltransferase 3B Involvement, Chromosome Anomalies, and Gene Dysregulation. Autoimmunity. 2008;41(4):253-71.
5. Polityko A. Two siblings with immunodeficiency, facial abnormalities and chromosomal instability without mutation in DNMT3B gene but liability towards malignancy; new chromatin disorder delineation? Molecular Cytogenetics. 2010;3(5):1-6.
6. Theisen A and Shaffer LG. Disorders caused by chromosome abnormalities. The Application of Clinical Genetics. 2010;3:159-74.

Cite this article as: Pande S, Bhushan M, Pais A, Pradhan G, Kadam C, Matkar S. Immunodeficiency, centromeric heterochromatin instability of chromosomes 1, 9, and 16, and facial anomalies: the ICF syndrome. Int J Contemp Pediatr 2017;4:1545-8.