CASE REPORT

Immunodeficiency, centromeric region instability and facial anomalies (ICF) syndrome diagnosed in an adult who is now a long-term survivor

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SUMMARY

We describe a 42-year-old British man of Indo-Caribbean origin with immunodeficiency, centromeric region instability and facial anomalies (ICF) syndrome. Most patients with ICF syndrome die of infection at a young age, usually in the first or second decade of life. The patient was born 3.5 weeks premature to non-consanguineous parents. He had a mild bird-like face abnormality, but had no other congenital malformations, cognitive impairment or developmental delays. He had recurrent ear and chest infections during childhood and developed bronchiectasis. Investigations revealed IgG, IgA and IgM deficiencies with a normal lymphocyte count and normal T cell proliferation to in vitro mitogenic stimulation. Following several unsuccessful attempts to make a diagnosis during childhood, a recent chromosomal analysis showed centromeric region instability of chromosomes 1 and 16, diagnosing ICF syndrome. The patient receives immunoglobulin replacement for hypogammaglobulinaemia and has chest physiotherapy and antibiotics for bronchiectasis. Recently, he developed liver cirrhosis of unknown cause.

BACKGROUND

In the late 1970s, cases of patients with immunodeficiency, facial anomalies and abnormalities of chromosomes 1, 16 and 9 were described^{1 2}; in 1988, the acronym ICF (immunodeficiency, centromeric region instability and facial anomalies) syndrome was proposed to describe the disorder's unique collection of features.³

At present, just less than 70 cases have been described⁴ and some progress has been made towards understanding the syndrome. In the past 15 years, mutations in DNMT3B and ZBTB24 genes have been found in patients with ICF syndrome.^{5 6}

ICF syndrome is a rare autosomal recessive disorder and a primary cause of hypo/agammaglobulinaemia or combined immunodeficiency⁷ and, as a result, patients usually present with recurrent infections during childhood. Most patients die at a young age, usually in their first or second decade of life.⁴

We describe the case of a British man of Indo-Caribbean origin who was diagnosed with ICF syndrome in his 30s.

CASE PRESENTATION

The patient was born 3.5 weeks premature, weighing 1900 g, to non-consanguineous parents. He was noted to have a bird-like face. Following birth,

he was intubated and managed in the paediatric intensive care unit for 3 weeks due to hypotonia and apnoea.

From a very young age, the patient suffered from frequent infections. He was described to be chesty from the start, getting coughs and colds and purulent conjunctivitis. At the age of 5 months, he suffered from an ear infection with frequent recurrences and at 9 months he developed a neck abscess. He also had hospital admissions for pneumonia. However, his growth and developmental milestones including cognitive development were normal. There was no significant family history of illnesses, but early deaths due to unknown causes in the non-immediate family were reported.

Investigations showed that the patient had hypogammaglobulinaemia (decreased IgG, IgA and IgM), but with a normal lymphocyte count and normal proliferation of T cells to phytohaemagglutinin. From the age of 2, the patient was given 2-weekly intramuscular immunoglobulin injections and long courses of antibiotics and regular chest physiotherapy. By the age of 7, he had developed significant bronchiectasis. He had a chronic productive cough, finger clubbing and crackles on lung bases on auscultation. *Haemophilus influenzae* was also isolated in his sputum.

INVESTIGATIONS

Analysis of sweat electrolytes and urine mucopolysaccharides was carried out to see if the patient had cystic fibrosis or Hurler syndrome, respectively, but these causes were ruled out. When the patient was in his early 30s, he had genetic tests to identify BTK gene mutations for X-linked agammaglobulinaemia, but this was negative. Finally, in his late 30s, he had a chromosomal analysis study which showed findings consistent with ICF syndrome (see table 1).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes the other causes of primary immunodeficiency such as Nijmegen breakage syndrome (NBS) and Bloom syndrome (BS).⁷ As with ICF syndrome, patients with NBS and BS can have facial anomalies, poor growth, psychomotor retardation and cognitive impairment. NBS and BS are also autosomal recessive diseases. However, patients with NBS or BS frequently have cancers, which are not as common in ICF syndrome.^{7 8}

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Table 1 Summary of the nature and frequency of chromosome 1 and 16 abnormalities on chromosomal analysis of the patient's peripheral blood cells (50 cells were analysed)

Chromosomal abnormality	Number of cells
Centromeric region breaks and deletions	2
Centromeric region decondensation	18
Multibranched chromosomes	17

OUTCOME AND FOLLOW-UP

The patient is currently under the care of haematologists and respiratory physicians for the management of immunodeficiency and bronchiectasis. He receives 6-weekly intravenous infusions of immunoglobulin (IVIG). The patient's IgG levels have been maintained between 10 and 16 g/L, although IVIG doses had to be increased. The IgA and IgM levels are undetectable (both are <0.25 g/L). Recently, the patient's lymphocyte count has decreased to $<1.0 \times 10^9/\text{L}$ which may suggest progression into combined immune deficiency; however, lymphocyte function testing has not been repeated following this decrease.

The patient continues to have chest physiotherapy and frequent antibiotics. Recently, sputum cultures grew *Pseudomonas* species. Current antibiotic therapy alternates between cotrimoxazole and doxycycline. In his adolescence, his peak flow was less than expected and later lung function tests showed signs of small airway disease with poor reversibility on using bronchodilators. The recent lung function tests have been stable (FEV₁ 1.28 L/min; forced vital capacity (FVC) 2.39 L). CT scans of the chest showed widespread bronchiectasis.

A new and outstanding issue for the patient is chronically deranged liver function tests. Over the past 10 years, the alkaline phosphatase level has been between 300 and 500 U/L and the alanine transferase level has been between 40 and 70 U/L (bilirubin is normal; protein is low-normal). A recent CT of the abdomen showed moderate ascites and a small liver of cirrhotic appearance. To date, a liver biopsy has not been performed. Granulomatous hepatitis or sclerosing cholangitis secondary to hypogammaglobulinaemia is suspected. Macronodular cirrhosis has been reported in two other patients with ICF syndrome; it was secondary to granulomatous hepatitis in one of the patients.⁴

DISCUSSION

ICF syndrome is diagnosed by standard chromosomal analysis of peripheral blood cells during metaphase. Cells will have instability in the form of, for example, deletions, breaks, elongation/decondensation, of the region adjacent to the centromere in chromosomes 1, 16 or 9. Other findings include multibranched chromosomes made up of duplicate arms of (usually) chromosome 1 and 16.⁸ Chromosomes 2 and 10 can also be affected, but this is not common.⁹

This region adjacent to the centromere (pericentromeric region) is made up of heterochromatin DNA, which is a methylated DNA that is tightly coiled and therefore appears dark/dense. DNMT3B is a DNA methyltransferase gene, and therefore mutations in this gene disrupt the process of transferring methyl groups to DNA. This gives rise to hypomethylated heterochromatin DNA, which manifests as the pericentromeric

region abnormalities that we see on chromosomal analysis in patients with ICF syndrome.⁸ However, it is unclear why the pericentromeric regions of other chromosomes are not affected in the same way.

Not all patients with ICF syndrome have DNMT3B gene mutations. The second gene found to be mutated in some patients with ICF syndrome, ZBTB24, belongs to a large group of transcriptional factors involved in haematopoietic development.⁶ ICF syndrome is now genotypically subclassified into patients with DNMT3B mutations (ICF1; Online Mendelian Inheritance in Man #242860), those with ZBTB24 mutations (ICF2; Online Mendelian Inheritance in Man #614069) or those with unknown gene mutations (ICFX). A genotype-phenotype correlation seems to exist in ICF syndrome: immunoglobulin deficiency seems more severe in ICF1 and intellectual impairment seems more severe in ICF2.⁴ Our patient did not have genetic testing to determine his gene mutation, but we would predict that he has ICF1. Gene testing was not carried out because it is unlikely to influence current management.

Most patients with ICF syndrome present with recurrent infections in early childhood, typically respiratory or gastrointestinal, which lead to bronchiectasis or failure to thrive and poor growth respectively.¹⁰ Recurrent infections in ICF syndrome are due to hypo/agammaglobulinaemia alone or combined immunodeficiency.⁷ In the former, patients have decreased levels of IgG, IgG subclasses, IgA, IgM or a combination of these. In the latter, they also have reduced lymphocytes and/or limited T cell proliferation to in vitro mitogenic stimulation.⁹ Several patients with ICF syndrome are reported to have had normal neutrophil, lymphocyte and platelet counts in childhood which then decreased in the second decade of life.⁴ This decrease in the lymphocyte and platelet (but not neutrophil) counts was observed in our patient too. (His neutrophil count is usually between 3.0 and $7.0 \times 10^9/\text{L}$; his haemoglobin level has also not decreased and is usually between 120 and 140 g/L.)

There are two reported cases of subclinical immunodeficiency where patients did not have problems with infections. Gimelli *et al* describe a case where ICF syndrome was diagnosed in a male adult with no history of recurrent infections, but who did have evidence of mild immunodeficiency upon investigation (reduced IgM, IgE and CD4 T cells). In fact, besides the subclinical immunodeficiency and characteristic chromosomal abnormalities, this patient had no other features of ICF syndrome. He was only diagnosed with it following the same diagnosis in his sister (who did have many features of ICF syndrome) which prompted investigations in the rest of her family.¹¹ Cerbone *et al*¹² also describe a patient with ICF syndrome with subclinical immunodeficiency (low IgM) and suggest that ICF syndrome could be more common than previously thought.

As in this case, patients with ICF syndrome are treated with IVIG and antimicrobials for infections. Bone marrow transplant has also been performed successfully in patients, but is not routinely performed. Prognosis is better in the absence of combined immunodeficiency. Common causes of mortality are opportunistic infections, respiratory infections and sepsis.^{8 10}

Most patients die at a young age, but this patient has survived into his 40s and might be the oldest known survivor of ICF syndrome. The current status of the brother (born in 1959) in the Gimelli *et al*⁴ case described above is unknown, and the sister (born in 1960) died of encephalitis at the age of 40 (a relatively advanced age of death).

Learning points

- ▶ Immunodeficiency, centromeric region instability and facial anomalies (ICF) syndrome is a rare, autosomal recessive disorder.
- ▶ Patients usually present with recurrent respiratory or gastrointestinal infections in childhood due to immunodeficiency (hypo/agammaglobulinaemia or combined immunodeficiency).
- ▶ ICF syndrome is diagnosed by chromosomal analysis which shows deletions, breaks, elongation/decondensation in the centromeric region of chromosomes 1, 16 or 9, and multibranched chromosomes. Mutations in two genes, DNMT3B and ZBTB24, are known to cause ICF syndrome.
- ▶ Patients are treated with intravenous infusion of gammaglobulin.
- ▶ Most patients die of infections in the first or second decade of life.

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Competing interests None.

Patient consent Obtained.

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