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Case Report

Immunodeficiency, centromeric instability and facial anomalies syndrome type 1-homozygous c.2301+2_2301+24del mutation in DNMT3B gene

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ABSTRACT

Immunodeficiency with centromeric instability and facial anomalies (ICF) syndrome is a primary immunodeficiency, predominantly characterized by agammaglobulinemia or hypoimmunoglobulinemia, centromere ICF. We present a case of a 3-month-old male infant was an inpatient in a district general hospital in East London with bronchiolitis requiring intravenous antibiotics and high flow oxygen therapy. He was discharged on day 12 of admission as clinically improving, however, he represented soon after discharge with worsening respiratory compromise. Intubation and transfer to a tertiary paediatric intensive care unit were needed. Subsequent investigations depicted neutropenia, anaemia and hypo-gamma-globulinaemia. A diagnosis of ICFS syndrome type 1 with mutation in DNMT3B gene was made.

Keywords: ICF syndrome, Hypo-gamma-globulinaemia, Immunodeficiency

INTRODUCTION

Immunodeficiency with centromeric ICF syndrome is a primary immunodeficiency, predominantly characterized by agammaglobulinemia or hypoimmunoglobulinemia, centromere ICF. Mutations in two genes have been discovered to cause ICF syndrome: DNMT3B and ZBTB24. This syndrome results in antibody deficiency as well as T-cell dysregulation and function disorder. Children with ICF1 deficiency are at higher risk of developing opportunistic infections, further autoimmune conditions and malignant disorders.[1]

CASE REPORT

A 3-month-old male infant presented to the paediatric emergency department of a district general hospital in central London with symptoms in keeping with bronchiolitis requiring intubation and transfer to a paediatric intensive care unit.

He was the first born to consanguineous (second cousins) parents of Bangladeshi origin. He was born at 36 weeks gestational age through emergency caesarean section in view of foetal distress. He required admission to the local neonatal intensive care unit in view of birth weight of 1555 grams. He had an uncomplicated stay and discharged home at 2 weeks.

Later in his life, at 1 month of age, he developed bronchiolitis requiring a 5-day admission to the paediatric ward, needing intravenous antibiotics and high flow oxygen therapy. In addition, at 3 months of age he developed fever associated with respiratory distress requiring hospitalisation. He was again treated with intravenous antibiotics and high flow oxygen therapy and was discharged on day 12. However, at the same day of

discharge he presented with worsening clinical picture. In more detail, the child started having frequent apnoeas and worsening blood gases leading to his intubation, ventilation and transfer to the tertiary paediatric intensive care unit. Subsequent investigations done revealed that he had profound neutropenia, anaemia and hypogammaglobulinaemia.

Investigations and treatment

The child was noted to have profound neutropenia, anaemia and hypo-gamma-globulinaemia which leads to the genetic diagnosis of ICF 1. Immunological investigations revealed pan hypo-gamma-glubulinaemia, low B and NK cells. He had normal naïve T-cells and HLH biomarkers. He had a video fluoroscopy done which showed mild-moderate oropharyngeal dysphagia.

He was treated with packed red cell transfusion for his anaemia. He was also given G-CSF for the neutropenia which he responded well. He was treated with intravenous immunoglobulin.

Currently, he continues to be on intravenous immunoglobulin every 3 weeks.

He is under the speech and language therapy team in view of unsafe swallow and is being nasogastric fed.

The child is under follow up with the paediatric immunology team. He has found a 10/10 match unrelated donor for haematopoietic stem cell transplant. His parents are keen to consider early transplantation.

DISCUSSION

Variants in the ZBTB24, DNMT3B, CDCA7, or HELLS genes may be the cause of ICF syndrome, an autosomal recessive condition. Though it is also linked to moderate facial dysmorphism, growth retardation, failure to thrive and psychomotor retardation, recurrent infections, primarily respiratory are the frequent presenting symptom. While most cases reveal weak antibody production, invasive fungal infections also show serious cellular dysfunction in some affected infants. Patients are vulnerable to bacterial and opportunistic infections due to typically low serum immunoglobulin levels, B cell and T cell counts, and immunoglobulin deficiencies.[2]

Not every ICF syndrome patient carries a mutation in the DNMTB3 gene. The second gene, ZBTB24, has been discovered to be altered in a subset of ICF syndrome patients. ZBTB24 is a transcriptional factor that is involved in the development of the hematopoietic system. In ICF syndrome, a link between genotype and phenotype appears to exist: immunoglobulin deficiency appears more severe in ICF1 and intellectual disability appears more severe in ICF2.[3] Our young patient was found to have a homozygous c.2301+2_2301+24del mutation in DNMT3B gene.

Approximately half of ICF cases have mutations in the DNA methyltransferase 3B gene (DNMT3B at chromosomal locus 20q11.2 (these cases are said to have ICF1). DNMT3B is one of the three main mammalian DNA methyltransferases that play an important but not exclusive role in de novo DNA methylation. In ICF1 patients, the enzymatic activity of DNMT3B is strongly, but not completely, reduced, and as a consequence, specific genomic regions of ICF patients show significant loss of DNA methylation.[3]

Most individuals with ICF syndrome initially show up with recurring infections in their early years, usually of the respiratory or gastrointestinal types, which cause bronchiectasis or stunted growth, respectively. Immunodeficiency paired with hypo or agammaglobulinemia is the cause of recurrent infections in people with ICF syndrome. Patients in the former group have reduced IgG, IgG subclasses, IgA, IgM, or any combination of these levels. In response to in vitro mitogenic stimulation, they also exhibit decreased lymphocyte counts and/or restricted T cell proliferation in the latter[4]. Our patient presented with recurrent respiratory tract infections in early life.

Like this instance, IVIG and antibiotics are used to treat infections in children with ICF syndrome. Although it is not commonly done, bone marrow transplants have also been successfully completed. In the absence of combined immunodeficiency, the prognosis is better. Sepsis, opportunistic infections, and respiratory infections are common causes of death.[4] In our child he was treated with IVIG.

In a large survey of 45 ICF syndrome patients, the age at diagnosis ranged from 5 weeks of life to 16 years, and 89% of cases were found to have hypo or agammaglobulinemia, recognized in early childhood.[5] In our patient, he was diagnosed at 3 months of age which is similar to this survey conducted.

In one case report a 8 year old child presented with intellectual disability, multiple café-au-lait spots, and a large cerebral arachnoidal cyst. Although laboratory signs of impaired immune function, such as reduced serum IgM were detected, our patient did not present with this.[6]

In a case report a familial case of ICF syndrome was described in a woman of 29 years and in her brother of 30 years. The proband showed mental retardation, facial anomalies, recurrent respiratory infections, combined deficit of IgM and IgE immunoglobulin classes, and paracentromeric heterochromatin instability of chromosomes 1, 9, and 16. The brother had minor signs of the syndrome and had an apparently normal phenotype. Their parents were healthy and non-consanguineous. Chromosome anomalies consisted of homologous and non-homologous associations, chromatid and isochromatid breaks, deletions of whole arms, interchanges in the paracentromeric region, and

multibranched configurations of chromosomes 1, 9, and 16. In our child, his parents were consanguineous.[7]

CONCLUSION

This is a classic case of a rare syndrome. This is a very typical and frequent presentation in infants of this age group-however, red flags such as multiple admissions and frequent infections should not be omitted. Complex cases such as this, require careful treatment prioritisation, planning and a full complement of specialist knowledge and expertise. Effective teamwork and communication between other team members, is essential to achieve safe and timely patient care.

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