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Presentation of DNA Methyltransferase 3 Beta Mutation with Immune Deficiency and Dilation of Aorta and Esophagus

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Abstract

Background: Immunodeficiency, Centromeric region instability, and Facial anomalies syndrome (ICF) is a rare autosomal recessive disorder with Centromeric instability as a hallmark.

Method: In this case report, we describe an Iranian 6-year-old male who was diagnosed with ICF syndrome. He had a history of recurrent infections, hydrocephalus report in pregnancy, failure to thrive, facial anomalies, global developmental delay, and umbilical hernia.

Results: The investigation showed esophageal dilatation in barium swallow, ascending aortic dilatation in echocardiography and cutis laxa in skin biopsy. In laboratory data, impaired antibody function was observed. Finally, to find the probable causative genetic variant, a whole exome sequencing was performed. The data analysis using bioinformatics tools revealed c.1592G>A mutation in the exon 15 of DNMT3B. With respect to the diagnosis of ICF syndrome, our patient was treated with intravenous immunoglobulin (IVIG).

Conclusion: It is necessary to perform periodic neurologic and ophthalmologic examinations. Echocardiography must be done annually. In addition, the possibility of HSCT should be evaluated.

Key Words: DNMT3B mutation, ICF Syndrome, Immune deficiency.

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1- INTRODUCTION

Immunodeficiency, Centromeric region instability, and Facial anomalies syndrome (ICF) is a rare autosomal recessive disorder with centromeric instability as a hallmark. This syndrome is characterized by variable combined immune deficiency, centromeric instability in chromosomes 1, 9, and 16, and facial anomalies (1-3).

This syndrome was described in the 1970s for the first time (4). The immunodeficiency in ICF patients is variable, ranging from severe immune deficiency to a near normal immune system. Most of the patients have a poor immune response with low or undetectable levels of immunoglobulin (5, 6). Facial anomalies in the ICF patients may include a round face with epicanthus, telecanthus, flat nasal bridge, hypertelorism, upturned nose, macroglossia, micrognathia, and low set ears (7). A high proportion of reported ICF patients have died from infection at a very young age. At present, just less than 80 cases with ICF syndrome have been reported (5, 8).

We describe an Iranian 6-year-old male who was diagnosed with ICF syndrome due to DNMT3B gene mutation. The patient presented with cutis laxa, dilated ascending aorta and lateral ventricle, significant esophageal dilatation, and brain atrophy.

2- CASE PRESENTATION

The patient is a 6-year-old Iranian male with consanguineous parents. He had a history of recurrent infections, and failure to thrive. He was admitted to the hospital when he was 5 days old with symptoms such as poor feeding, vomiting, weight loss, and icter. No source of infection was detected based on the sepsis workup. With respect to hydrocephalus report in pregnancy, mild dilatation of lateral and third ventricles was observed in his brain Computed Tomography (CT) scan (**Fig. 1**).

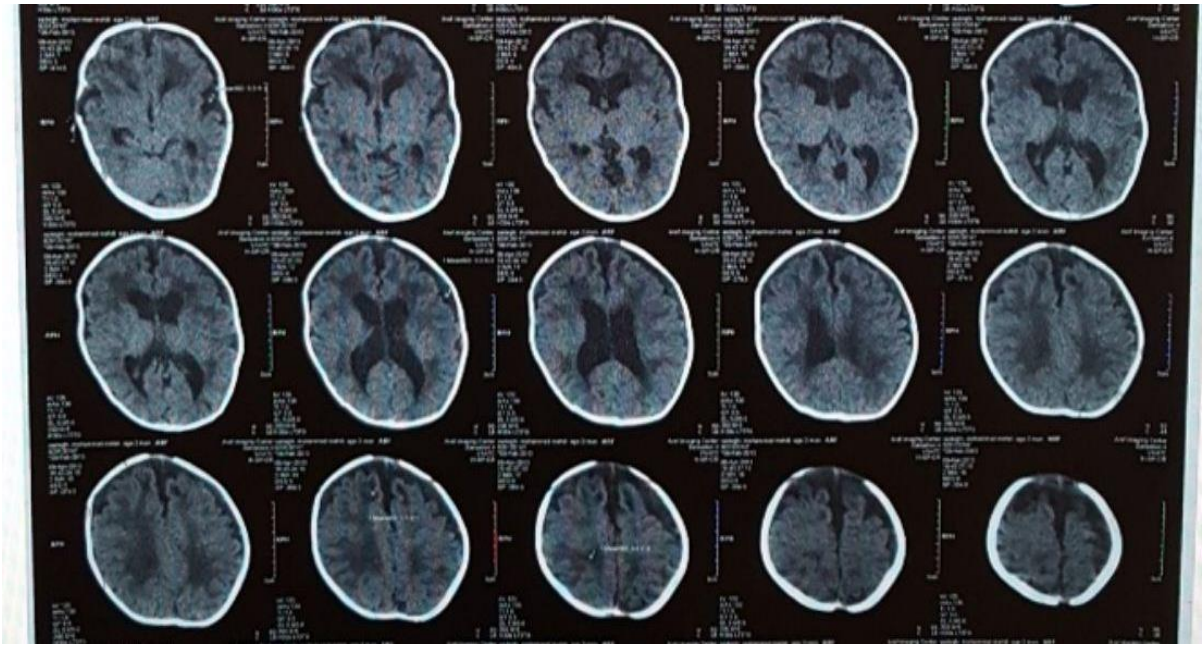

Fig. 1: Non-contrasted spiral computed tomography scan; dilatation in ventricles, frontotemporal atrophy, and periventricular hypodensity

The patient had facial anomalies, such as flat nasal bridge, hypertelorism, bilateral ptosis, upturned nose, and low set ears. Moreover, the patient suffered from hypotonia and a global developmental delay, including delays in motor, language, and social development. In addition, he was not able to walk until he was 3 years old. On physical examination, he was diagnosed with an umbilical hernia from birth, and growth parameters showed a failure to thrive. At the age of 6, the patient had a body weight of 14kg (0.1 percentile) and a height of 110 cm (15th percentile) based on the centers for disease control and world health organization growth charts.

The patient suffered from recurrent infections from birth and gastroenteritis, otitis media with otorrhea, and sinusitis at the age of 13 months, 1, and 4 years, respectively. He was admitted to hospital at the age of 4 with chronic cough (longer than 4 weeks) and pneumonia. Barium swallow test was done with respect to chest radiography and probability of aspiration. The results showed esophageal dilatation leading to the diagnosis of esophageal dysmotility (**Fig. 2**). Endoscopy and biopsy were done through gastroenterology service. Based on the total evidence, genetic testing was suggested but his parents conducted it after one year.

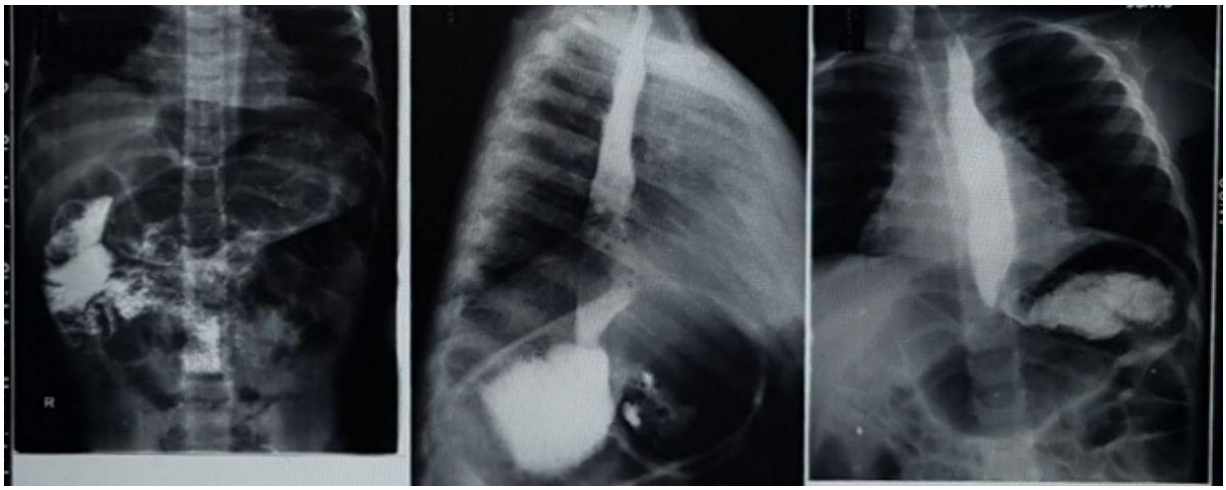

Fig. 2: Barium swallow test showing esophageal dilatation

3- INVESTIGATIONS

Tandem Mass Spectrometry (MS/MS) was performed due to hypotonia and abnormal face. We observed normal results when the patient was at the age of 10 days. Dilatation in ventricles, frontotemporal atrophy, and periventricular hypodensity were found according to the control CT-scan of the brain at the age of 2 months old.

Electroencephalography demonstrated paroxysmal sharp waves. The results of electromyography and nerve conduction velocity tests were normal. At the age of 15 months, the ophthalmologic examination was performed due to bilateral ptosis and strabismus. Accordingly, intermittent exotropia was detected with the recommendation of patch therapy.

At his age of 2 years old, echocardiography was done and the results showed ascending aortic dilatation, floppy mitral and tricuspid valve without any mitral and tricuspid regurgitation.

Moreover, control echocardiography was performed annually.

The patient was 4 years old at the time of hospital admission, and a pneumonia sweat test was performed due to failure to thrive. The obtained results were normal in all of the three times.

According to the CT scan findings, the consolidation in left lower lobe, lingula, right middle and lower lobe, and pan-sinusitis were observed in the thorax and paranasal sinuses.

Due to skin laxity, a skin biopsy was performed when the patient was 4 years old (**Fig. 3**). The histopathology of the skin biopsy was in favor of a clinical diagnosis of cutis laxa. The serum copper level was 0.245 mg/L (below the normal range 0.474 - 0.749 mg/mL).

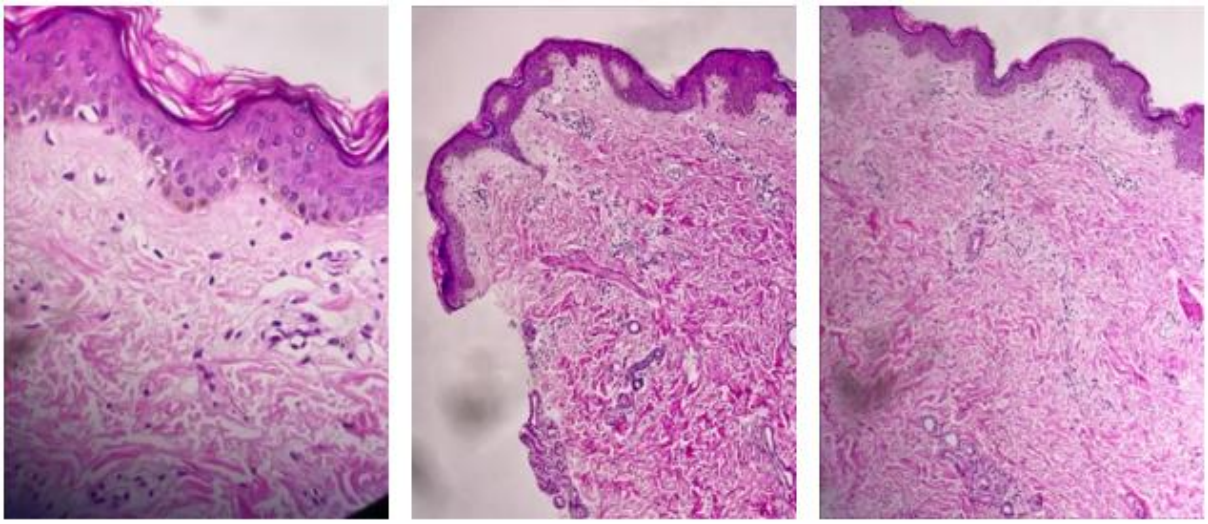

Fig. 3: Histopathology of the patient's skin biopsy

Endoscopy reports at the age of 3 showed significant dilatation with tortuosity in esophagus and nodularity and fragility in the duodenum. Pathology results of the biopsy were normal which led to the exclusion of celiac disease. Laboratory markers (**Table 1** and **Table 2**) showed normal white blood cell counts and immunoglobulin levels. However, antibody function was impaired and the patient received intravenous immunoglobulin (IVIG) monthly.

Table-1: Complete blood count results of the patient

Parameter	Value
WBC (1000/mm3)	8.2*
RBC (million/mm^3)	4.7
Hb (gr/dl)	11.8
Hct (%)	36.7
MCV(fl)	76.8
MCH (pg)	24.7
MCHC (g/dl)	32.2
Plt (1000/mm3)	352

Table-2: Results of the immunological test

Parameter	Value
Anti A	Negative
Anti B	Negative
Blood group and Rh	O+
NBT test	98%
Tuberculin test	1mm
CH50 (U/ml)	51
HBS Ab (mlu/ml)	10
IgM (mg/dl)	178
IgG (mg/dl)	724
IgA (mg/dl)	106
IgE (IU/ml)	206

Finally, to find the probable causative genetic variant, a whole exome sequencing was performed. Data analysis using bioinformatics tools revealed c.1592G>A mutation in the exon 15 of DNMT3B in patients with ICF1. This genetic variant changes Arginine to Histidine at codon 531 (p.Arg 531 His).

4- DISCUSSION

Inborn errors of immunity are a heterogeneous group of disorders which predispose patients to a wide range of unusual features, including recurrent infections, malignancy and autoimmune diseases. Due to this variety of presentations, every unusual infection in terms of intensity or microorganisms, and/or manifestations of immune dysregulation as early onset or multiple autoimmune disorders, and also frequent malignancies could be associated with primary immune deficiencies (9, 10). In this case report we aimed to describe a six-year-old boy who referred to us with multiple disorders and an abnormal face. In his medical history, he had frequent bacterial Sino pulmonary infections, neurodevelopmental Daley, hypotonia and failure to thrive. Investigations showed esophageal dilatation in barium swallow, ascending aortic dilatation in echocardiography and cutis laxa in skin biopsy. In laboratory data, impaired antibody function was observed. Finally, to find the probable causative genetic variant, a whole exome sequencing was used; and the data analysis using bioinformatics tools revealed c.1592G>A mutation in the exon 15 of DNMT3B. After receiving monthly intravenous immunoglobulin, his infection courses were attenuated. And now after three years of follow-up, he is in a good condition without any more hospitalization due to infection.

Almost 50% of the patients with ICF are classified as ICF1. They have been found with mutations in the DNMT3B gene which is located on the long arm of chromosome 20 at position 11.2 (11). Dysmorphic features in the face are reported in nearly all patients. Some of these facial dysmorphic features, especially in DNMT3B mutation, are hypertelorism, flat nasal bridge, epicanthus, and round face (5). However, no patient with DNMT3B mutation was reported with cutis laxa until now. Low level of serum copper in the patient could lead to diminished elastin synthesis and consequently cutis laxa.

Sathasivam et al., in a case study, investigated a 42-year-old British male with ICF syndrome. The patient suffered from frequent infections from a very young age. He had developed significant

bronchiectasis at the age of 7. They did not perform genetic testing; however, they predicted that the patient had ICF1. Their results showed that the patient had hypogammaglobulinemia; however, his lymphocyte count was normal. From the age of 2, the patient received IVIG (12).

In 2017, Gossling et al. reported a 1-year-old Moroccan male who was diagnosed with ICF1 syndrome at the age of 4 months. He suffered from recurrent respiratory and gastrointestinal infections. At the age of 6 months, the patient underwent Hematological Stem Cell Transplantation (HSCT) from his healthy 5-year-old sister as a donor. They found that early diagnosis and subsequent HSCT could prevent severe infections that led to the treatment of the immunodeficiency (13). In 2018, Kamae et al. studied eleven Japanese patients with ICF syndrome. The results indicated that the patients with ICF syndrome had a phenotype of combined immunodeficiency, thus, suggesting that they should receive immunoglobulin replacement therapy to achieve a better prognosis (2).

5- OUTCOMES AND FOLLOW UP

With respect to the diagnosis of ICF syndrome, our patient was treated with IVIG every 4 weeks. In order to evaluate his respiratory state, pulmonary function tests should be done and the patient must be under clinical follow-up. Moreover, it is necessary to perform periodic neurologic and ophthalmologic examinations. Due to the involvement of the aortic valve, echocardiography must be done annually by a pediatric cardiologist. In addition, the possibility of HSCT should be evaluated by a pediatric hematologist.

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