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Immunodeficiency, Centromeric Instability, and Facial Dysmorphism (ICF) Syndrome: How HSCT alters the impairment of the DNA methylation process

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Abstract

Introduction and purpose

In 2024, the EBMT Inborn Errors Working Party published a study that confirmed the beneficial role of hematopoietic stem cell transplantation (HSCT) in patients with immunodeficiency, centromeric instability, and facial dysmorphism (ICF) syndrome. In this article, we aim to present the characteristics of ICF in an accessible way, including its genetic background, clinical presentation, immunological alterations, and treatment options.

A brief description of the state of knowledge

In recent years, published reviews and series of cases have expanded the range of known symptoms and complications occurring in patients with ICF. Our understanding of immunological alterations in ICF evolved from isolated defects of immunoglobulin production to a comprehensive model which involves impairment of cellular immunity. Advances in molecular biology and genetics enabled insights into the DNA methylation machinery, which allowed us to gain a more precise understanding of the pathogenesis of ICF and also opened up opportunities for the development of new therapeutic options.

Summary

Inborn errors of immunity (IEI), such as ICF, are diagnosed at an early stage of life. It enables effective treatment with longer survival of the patients. It means that healthcare professionals are increasingly likely to encounter such patients in their clinical practice. Thus, it is crucial to inform

about the usage of the HSCT in ICF syndrome and spread awareness of potential new treatment options, that may emerge in the near future.

Keywords: Immunodeficiency–centromeric instability–facial dysmorphism (ICF) syndrome; Inborn Errors of Immunity; Hematopoietic stem cell transplantation; Combined immunodeficiency

Introduction

Immunodeficiency, centromeric instability, and facial dysmorphism (ICF) syndrome is a group of rare autosomal recessive inborn errors of immunity (IEI) [1]. The first report of the ICF was published by Hulten et al. in 1978 [2]. Since then, slightly over one hundred cases have been reported worldwide [1,3]. The molecular mechanism of ICF development lies in the impairment of the epigenetic process of the development and maintaining DNA methylation pattern [4–6]. The core symptoms of ICF are immunodeficiency of variable extent, mild facial anomalies, and neurologic impairment [7]. Despite the shared core of the clinical and molecular similarities, ICF is a group of diseases with various genetic backgrounds. Two of the most often diagnosed types of ICF, which encompass over 80% of all reported cases, are ICF1 with a mutation in the *DNA methyltransferase 3B* (*DNMT3B*) gene and ICF2 with a mutation in the *zinc-finger and BTB domain containing 24* (*ZBTB24*) gene [1,8]. Other subtypes are ICF3 and ICF4 with the mutations in the *cell division cycle associated 7* (*CDCA7*) and *helicase lymphoid specific* (*HELLS*) genes respectively [9]. There was also established an ICF X category for patients who present clinical symptoms of ICF with yet unknown genetic aberrations [5]. In recent years, there have been published articles, that present a more accurate molecular landscape of the DNA methylation process, thanks to the usage of Clustered Regularly-Interspaced Short Palindromic Repeats/Cas 9 (CRISPR/Cas9) machinery. It has also led to a deeper understanding of the molecular mechanism underlying the pathogenesis of ICF [10–13]. From the clinical point of view, in 2024 the EBMT/ESID Inborn Errors Working Party published its first recommendations on the treatment of ICF with the usage of Hematopoietic stem cell transplantation (HSCT) [14]. Given these significant scientific advances regarding ICF, we aim to provide a clear and accessible overview of this group of disorders for clinicians who may encounter them in their practice [15].

Material and methods

Articles cited in this manuscript were searched using keywords: Immunodeficiency–centromeric instability–facial dysmorphism syndrome, ICF, inborn errors of immunity, IEI, DNMT3B, ZBTB24, CDCA7, and HELLS in databases including PubMed, Scopus, and Springer Nature.

Genetic Background

The molecular hallmarks of ICF include instability of the juxtacentromeric heterochromatin regions of chromosomes 1, 9, and 16 enriched with specific hypomethylation of pericentromeric satellite repeats 2 and 3 [16]. It results in whole-arm deletions, chromatid, and chromosome breaks, stretching, and multiradial chromosome junctions observed in phytohemagglutinin (PHA)-stimulated lymphocytes [3,4,7,17]. This flaw is associated with disturbances in the epigenetic modification process of methylation of the CpG-rich (ICF1), and -poor (ICF2-4) promoter regions, and it is responsible for the development of all known forms of the ICF [4,5]. DNMT3B's main role lies in establishing a DNA methylation pattern during embryogenesis [4]. ICF1 patients carry missense, nonsense, or splice-site mutations of the *DNMT3B* gene on chromosome 20q11.2, that impair the catalytic part of methyltransferase [4,18,19]. However, they do not lead to a complete loss of enzyme activity, as such a loss could be lethal for humans [18]. This impairment results in promoter hypomethylation of germline genes and loss of methylation at X-linked genes [11,20–22]. In the case of ZBTB24, CDCA7, and HELLS, these are the part of DNA methyltransferase 1 (DNMT1) - dependent maintenance pathway, which preserves established methylation patterns throughout the lifetime [4,23]. ICF2 arises from nonsense and frameshift mutations in the *ZBTB24* gene located on chromosome 6q21, which causes premature termination of the protein [5,24–26]. Patients with ICF3 carry missense mutations of the *CDCA7* gene on chromosome 2q31.1, that impair the function of its conserved C-terminal zinc finger domain. In the case of the ICF4, various mutations of the *HELLS* gene on chromosome 10q23.33, disturb its function as a member of the SNF2 Family of ATP-dependent chromatin remodelers [9,12,27–30].

ZBTB24's role in the development of the ICF is connected with the HELLS-CDCA7 nucleosome remodeling complex, as it serves as a transcriptional factor that positively regulates the expression of CDCA7 [5,31]. CDCA7 enables the recruitment of HELLS to chromatin and supports its nucleosome remodeling activities [27]. Dysregulation of the CDCA7-HELLS complex directly disturbs access of DNA methylation machinery to genomic regions [9,27,31]. Mutations present in Patients with ICF2, ICF3, and ICF4 were also proven to impair classical nonhomologous end-

joining (c-NHEJ), which disturbs V(D)J recombination and class-switch recombination (CSR) in lymphocytes, which might be crucial in the pathogenesis of immunodeficiency [25,32,33]. Additionally, in patients with each form of the ICF, who presented an atypical course of the disease, mutations of Ubiquitin-like containing PHD and RING finger domains 1 (UHRF1) have been confirmed [13,23].

At the molecular level, the distinction between ICF1 and ICF2-4 lies in the methylation status of centromeric α-satellite and subtelomeric repeats. In ICF1, centromeric α-satellite repeats exhibit normal methylation levels, while in other ICF subtypes these regions demonstrate a hypomethylation [34]. For subtelomeric repeats the situation is reversed: ICF1 patients exhibit hypomethylation, whereas patients with other ICF types present standard methylation levels [20]. DNA methylation has a crucial function in transcriptional regulation, silencing of transposable elements, genomic imprinting, and X-chromosome inactivation. Disruption of this epigenetic process profoundly affects the functioning of the entire organism [16].

Alterations in development and physical appearance

The most characteristic clinical features of ICF patients are a wide range of congenital facial abnormalities. However, they are variable and usually mild. The most commonly observed are hypertelorism, flat nasal bridge, and epicanthic folds [8,17,35]. Other alterations encompass a round face, macrocrania, high forehead with frontal bossing, up-turned nose, low-set ears, micrognathia, macroglossia, cleft palatine, or lip [7,8,17,35]. Other characteristics of the ICF are limb deformations, such as short and thin limbs, clinodactyly, and syndactyly. Other described alterations include hypospadias, protruding abdomens, bipartite nipples, and skin pigment changes [1,35,36]. Among the changes in internal organs, the following have been listed: atrial septal defect, ventricular septal defect, ascending aorta dilatation, and horseshoe kidney [7,8,35,36]. Several patients have been described with cerebral malformations, such as corpus callosum hypoplasia, macrocephaly, and cortical atrophy [7,8,35]. It is worth mentioning, that most of the listed above non-facial changes were reported in isolated cases. In the neonatal period, patients may present with prematurity, low birth weight, and failure to thrive [1,8]. ICF also affects psychomotor development, as the majority of ICF patients exhibit a delay in walking and speech. It also leads to psychomotor impairment in the form of ataxic gait, muscle hypotonia, and seizures [7,36]. Patients may also show signs of growth retardation, which is suspected to be associated more with low birth weight and recurrent gastrointestinal infection, than with the underlying genetic defect [7]. When it comes to the intellectual status of the patients, the picture is variable. Mental disability from mild to severe was

described in almost all ICF2 patients. In comparison, more than half of the ICF1 patients exhibit normal intelligence [1,8,35]. Such a differentiation might be connected with ZBTB24's high expression in the caudate nucleus and its role in the differentiation of the hippocampal neurons, as both structures are an essential part of the brain's learning and memory system [8,37].

Immunological alterations

The typical immunological deficiency in patients with ICF was described as hypo- or agammaglobulinemia, which is one of the first noticed features of the disease, diagnosed at a median age of 3 years [15,35]. However, the alterations, do not involve solely immunoglobulin production. While the number of lymphocyte B cells remains on the standard level, immunophenotyping confirms a low level of memory B cells in all ICF patients [1,35]. Despite the general immunological landscape seems similar in all ICF patients, there are some significant differences between them. When it comes to the number of CD19+ CD27+ memory B cells their level is significantly higher in ICF1 patients compared to ICF2 patients. In the case of the number of circulating immunoglobulins, due to more severe impairment in the process of immunoglobulin class-switch recombination, ICF1 patients also present significantly lower levels of IgG and IgA in serum [1,25,35]. While ICF was commonly associated with isolated humoral immunodeficiency, recently published studies support the presence of dysregulations in cellular immunity. In ICF patients decreased number of CD4+ lymphocytes type T cells, with abnormal CD8+/CD4+ ratio was noticed. Changes were observed in lymphocyte T differentiation, with a higher number of T_{FH} and a lowered population of T_{FR} and Treg lymphocyte subtypes [38]. Also, impaired proliferation capacity of both CD4+ and CD8+ lymphocyte T was confirmed. A reduction in the number of NK cells was also observed. These findings support the existence of a combined immunodeficiency in patients with ICF syndrome [38–40]. Interestingly, abnormalities in T lymphocyte counts were detected in patients at a later stage of life [8]. Despite progress in our understanding of the mechanism of immunodeficiency in ICF, direct links between specific mutations and impaired immunological function remain unclear [15]. In the case of hypo- or agammaglobulinemia, the suspected mechanism is impairment of the class-switching process and dysregulation of immunoglobulin signaling, while the direct mechanism underlying cellular immune dysfunction remains a subject of ongoing investigation by researchers [15,25,35,41]. The natural consequences of combined immunodeficiency are recurrent infections and increased incidence of bacterial sepsis, which are leading causes of premature death, that usually occur in the first or second decade of life [1,7,41]. The most common include respiratory (bronchitis, otitis) and gastrointestinal tract

infections, which are noticed at the median age of 4 months [8,35]. Most infections are either viral or bacterial; however, the presence of opportunistic pathogens, such as *Candida* spp. or *Pneumocystis jiroveci* is a common finding [1,7,8]. Additionally, the presence of JC polyomavirus infection, as well as EBV and CMV viremias were regularly reported [1,42]. In a few patients, there were confirmed EBV-driven malignancies, such as diffuse large B cell lymphoma, and hemophagocytic lymphohistiocytosis [38,43]. Differences in the immunological landscape in ICF1 and ICF2 patients are reflected in the infectious complications they experience. While the frequency of bacterial and viral infections in both groups of patients remains at the same level, sepsis and fungal infections are more commonly observed in ICF1 patients [1]. Such differences may arise from more profound hypogammaglobulinemia and impairment of lymphocyte T-cell function in those patients [38]. There are also multiple reports of immunologic diseases found in ICF patients, such as: gastritis, enteropathy, colitis, hepatitis, inflammatory bowel disease, thyroiditis, pulmonary alveolar proteinosis, and non-septic arthritis [7,15,35,44–46]. Another group of disorders commonly associated with ICF are the hematologic ones, which include iron-deficiency anemia, aplastic anemia, thrombocytopenia, leukocytopenia, myelodysplastic neoplasm, acute lymphoblastic leukemia, and Hodgkin lymphoma [7,15,35,45].

Treatment options and recommendations

Symptomatic methods of treatment of ICF involve immunoglobulin substitution and antimicrobial prophylaxis, which help protect patients from recurrent infections [7,47]. However, this therapeutic approach is not a solution without flaws, such as the necessity of continuous administration of the drug throughout a lifetime, preserving consequences of impaired lymphocyte T cell function, and persistent defects in mucosal immunity that manifest as persistent diarrhea [35,48,49]. The imperfection of antimicrobial prophylaxis resulted in shortened lifespan of the patients [8]. Since Gennery et al. 2007 and Hagleitner et al. 2008 presented cases of patients with ICF1 syndrome successfully treated with HSCT, it has been postulated, that it can reverse humoral and cellular immunodeficiency associated with ICF [7,47]. Previous recommendations of IEI treatment did not address its performance in patients with ICF, despite several cases, which presented promising results [8,35,43,50–52]. It changed in 2024 when Berghuis et al. published an official study on behalf of the EBMT/ESID Inborn Errors Working Party Study, that encouraged clinicians to perform HSCT in patients with all types of ICF syndrome [15]. The overall survival in their cohort of 18 patients with ICF treated with HSCT cohort was 83%. All deaths occurred within the first few post-HSCT and all of them were due to infections. Until the latest follow-up Patients,

who survived the procedure, presented cellular immune reconstruction in CD3+, CD4+, and CD8+ lymphocytes T and NK cells approximately on the level of 90% within the age-adjusted reference values. A number of lymphocyte B cells were within the age-adjusted reference values in all cases. Patients who survived HSCT achieved resolution of pre-transplantation infections and immune dysregulation including non-infectious enteropathy and malignancy [15]. This study also confirmed conclusions drawn from the case published by Kraft et al., that achieving stable mixed chimerism leads to complete immune reconstitution [15,52]. It has an important indication, as it may encourage clinicians to use a reduced-intensity conditioning schemes are characterized by better toxicity profiles and a lower rate of occurrence of GvHD [53,54]. Another important message is that more beneficial aspects of HSCT are observed in patients transplanted in early childhood, compared to the older ones, as they suffer from irreversible bronchiectasis, immune-mediated organ damage, and malignancies [15,35,51]. ICF diagnosis, alongside clinical presentation, is based on cytogenetic analysis and gene panel sequencing, so broader access to those techniques may contribute to faster diagnosis and better outcomes of transplantation [3,55]. There were also attempts to use the detection of T Cell Receptor Excision Circles (TREC), which is successfully incorporated into the diagnostic process of other immunodeficiency syndromes, however, it has been proven ineffective in the diagnosis of ICF [56]. Although HSCT reverses the negative consequences of immunodeficiency and hematological impairment, it does not reverse delays in neurological development or cortical atrophy associated with seizures [7,8].

Conclusions and Future Perspectives

ICF remains a rare example of a disease caused by the disorder of the DNA methylation process resulting from a single gene defect [11]. The discovery that impairment of this epigenetic process is a background of the severe and potentially fatal syndrome has led to investigations of its presence in other diseases, such as autoimmune and metabolic diseases, solid tumors, and hematological malignancies [11]. The future of therapeutic approaches to the impairments of methylation machinery may lie in using CRISPR/Cas9 technology. Currently, it is being utilized to create an induced pluripotent stem cells (iPSCs) model for ICF cells, however, some publications explore the usage of this technology to correct methylation aberrations encountered in those cells [10,57]. Considering that, currently in clinical use, there are approved anti-cancer drugs that affect DNA methylation, it implies that progress in the usage of CRISPR/Cas9 may provide new curation possibilities for patients with ICF syndrome [11,58].

Disclosures

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