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ORIGINAL ARTICLE

Genetic, Cellular and Clinical Features of ICF Syndrome: a French National Survey

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Abstract
Purpose Autosomal recessive deficiencies of *DNMT3B* or *ZBTB24* account for two-thirds of cases of immunodeficiency, centromeric instability and facial dysmorphism (ICF syndrome). This primary immunodeficiency (PID) is characterized mainly by an antibody deficiency, facial abnormalities and centromeric instability. We analyzed the national cohort of patients with ICF syndrome with the aim of providing a more detailed description of the phenotype and management of patients with ICF syndrome.
Methods Demographic, genetic, immunological, and clinical features were recorded for each patient.
Results In the French cohort, seven of the nine patients carried *DNMT3B* mutations, six of which had never been described before. One patient had compound heterozygous *ZBTB24* mutations. All patients were found to lack $CD19^{+}CD27^{+}$ memory B cells. This feature is a major diagnostic criterion for both ICF1 and ICF2. Patients suffered both bacterial and viral infections, and three patients developed bronchiectasis. Autoimmune manifestations (hepatitis, nephritis and thyroiditis) not previously reported in ICF1 patients were also detected in two of our ICF1 patients. The mode of treatment and outcome of the French patients are reported, by genetic defect, and compared with those for 68 previously reported ICF patients. Immunoglobulin (Ig) replacement treatment was administered to all nine French patients. One ICF1 patient presented severe autoimmune manifestations and pancytopenia and underwent allogeneic hematopoietic stem cell transplantation (HSCT), but she died from unknown causes 6 years post-transplant.
Conclusion Autoimmune signs are uncommon in ICF syndrome, but, when present, they affect patient outcome and require immunosuppressive treatment. The long-term outcome of ICF patients has been improved by the combination of IgG replacement and antibiotic prophylaxis.

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Keywords ICF syndrome · primary immunodeficiency · memory B cells · centromeric instability · autoimmune disease

Abbreviations

AR	autosomal recessive
DNMT3B	DNA methyltransferase 3B
ENT	ear-nose-throat
HSCT	hematopoietic stem cell transplantation
ICF	immunodeficiency, centromeric instability, facial anomalies
IVIG	intravenous immunoglobulin
P	patient
PID	primary immunodeficiency

Introduction

The immunodeficiency-centromeric instability-facial anomalies (ICF) syndrome is a rare autosomal recessive (AR) disorder, first described in 1978 [1]. Most patients have mild facial anomalies and delayed developmental milestones, with various degrees of cognitive impairment. They present with recurrent infections due to profound panhypogammaglobulinemia, with no detectable impairment of immunoglobulin (Ig) class-switch recombination in vitro [2], a lack of memory ($CD19^{+}CD27+$) B cells in peripheral blood and a variable cellular deficiency [3]. Only a limited number of studies have explored T-cell function in these patients, despite suggestive infections and evidence for T-cell abnormalities in mouse models of ICF [4]. Rearrangements of chromosome structure associated with DNA hypomethylation in the heterochromatic regions of chromosomes 1, 9 and 16 are a hallmark of this disease [5–8]. About 50 % of patients carry AR mutations of the DNA methyltransferase 3B (*DNMT3B*) gene and are considered to have ICF type 1 [9, 10]. These mutations mostly affect the catalytic activity of the enzyme, significantly modifying the DNA methylation landscape and, thus, the expression of many genes, including some critical for immune function and development [11]. AR *ZBTB24* mutations have been found in almost 30 % of the remaining ICF patients. These patients are considered to have ICF type 2 [12]. ZBTB24 belongs to the zinc finger and BTB domain family of transcription factors, several of which are involved in various stages of B-cell differentiation [13, 14]. The function of ZBTB24 is unknown, but this protein has been localized to heterochromatin and may be involved in controlling heavily methylated regions [15]. Clinically, intellectual disabilities are the most marked signs in ICF2 patients, whereas antibody deficiency tends to be more pronounced in ICF1 patients [16]. More recently, ICF3 and ICF4 patients have been described with mutations in *CDCA7* and *HELLS*, emphasizing the genetic heterogeneity of this syndrome [17].

Since 1978, up to 70 ICF patients have been reported in individual case reports, national or international series [1, 3, 12, 15, 16, 18–50]. However, the nature and severity of the infectious events, the impact of prophylaxis, age at diagnosis and clinical outcome remain poorly characterized. In the face of the heterogeneity of the features of ICF syndrome, we decided to carry out a thorough clinical, immunological and genetic description of the largest national cohort reported to date, comprising nine ICF patients included in the French registry (CEREDIH) for primary immune deficiencies. We also document the first described cases of autoimmune signs in ICF1 patients and highlight the impact of prophylaxis on the clinical outcome of the patients.

Methods

Patients and Clinical Definitions

The patients consulted at various French hospitals and were identified through the CEREDIH (*Centre de Référence des Déficits Immunitaires Héréditaires*) at Necker Children's Hospital, Paris, France. The physicians caring for the patients completed a detailed questionnaire; clinical and biological data were collected from birth until August 2015. The median age of the cohort at the time of the study was 15 years (range: 8 months to 34 years). Approval for this study was obtained from the institutional review board of Necker Hospital and informed consent was obtained from all patients or their families (for minors), in accordance with the Helsinki Declaration (CNIL authorization: no. 908,256, October 14th, 2008).

Genetic Analysis

Genomic DNA was prepared from the blood samples of patients by the standard phenol-chloroform extraction method. The exons of *DNMT3B* and their flanking intron sequences were amplified by PCR with specific oligonucleotide primers (available on request) and sequenced with the Applied Biosystems Big Dye terminator kit v1.1 (AB Foster City California) and an ABI Prism 3130xl Analyzer (Applied Biosystems). PolyPhen-2 (polymorphism phenotyping) (http://genetics.bwh.harvard.edu/pph2/), a bioinformatics method for predicting the possible impact of an amino-acid substitution on the structure and function of a protein, was used to estimate the effect of the newly identified mutations. Mutations in *ZBTB24* and *CDCA7* were identified as described in [15, 51].

Immunological Investigations

Immunological investigations were based on those described in previous studies and/or the questionnaires sent to physicians [52, 53]. All antibody determinations were performed

before Ig treatment. The normal ranges for lymphocyte numbers and Ig levels were determined from laboratory data [54].

Statistical Analysis

The data were analyzed with Microsoft Excel® and GraphPad Prism® software. When necessary, data were compared in Mann-Whitney tests. A p value <0.05 was considered significant.

Results

Epidemiologic Features of the Cohort

We studied nine ICF syndrome patients from eight kindreds (6 female and 3 male patients). All but two (P7 and P8) of the patients were alive at the time of reporting, after a median follow-up of 7.5 years. P6 is lost from follow-up. Five patients were born to consanguineous parents (Table 1).

We identified AR mutations of *DNMT3B* in seven of the nine patients. We found homozygous *DNMT3B* mutations in four consanguineous kindreds, and compound heterozygote mutations in the other three patients. Five mutations were missense mutations (c.1747G > A, c.1964C > T, c.2162 T > C, c.2324C > T, c.2450 A > G) affecting amino acids located in the catalytic domain of the DNMT3B protein and were classified as "probably damaging" by polyPhen-2. Others were nonsense mutations (n = 2, c.C310T and c.158dupT) or splice-site mutations (n = 3, c.143-22del, c.1252 + 13 T-G and c.2302-212 T > C). A composite heterozygous mutation of *ZBTB24* was described in P4 (c.A787T/980_981delGT) [15]. Patient P6 carried a homozygous mutation in *CDCA7* (c.911G > A) [17]. The details are presented in Table 1.

The first clinical signs, mostly recurrent infections (n = 6) or a failure to thrive (n = 3), occurred at a median age of 4 months (range: 1 to 12 months). Hypogammaglobulinemia was diagnosed at a median age of 3.3 years (range: 2 months to 11 years), whereas the diagnosis of ICF on the basis of cytogenetic hallmarks occurred at a median age of 5.2 years (range: 1 month to 11.4 years). We assessed the typical facial anomalies in each patient, as reported at diagnosis. The following abnormalities were found: high forehead with frontal bossing (P3, 5 and 7), hypertelorism (P3, 5 and 7), epicanthus (P7 and P8), low-set ears (P3 and 7), macroglossia (P3 and 7). A few other abnormalities, including hyperpigmented spots (P5), macrocrania (P5), sparse hair (P5) and short limbs (P7), were also recorded. No dysmorphic features were reported for three patients at diagnosis and later during childhood (Table 1). Clinical examination revealed hypospadias in one ICF1 patient (P3). This malformation has already been reported in ICF patients [3].

Delayed Growth and Mental Retardation

Five (P1, 2, 6, 7 and 9) of the patients with adequate birth records had birth weights below the 10th percentile, and three patients (P2, P6 and P9) had birth heights below the 10th percentile. Eight patients displayed a failure to thrive, at a mean age of 4.5 months (range: 3 months to 10 years). One of these patients (P3) required growth hormone treatment and the failure to thrive of two other patients was related to chronic diarrhea. Gastrointestinal problems were common in our ICF patients (n = 6). For instance, P3 had two episodes of *Salmonella* sp. gastroenteritis requiring hospitalization and fluoroquinolone treatment before Ig replacement. Three patients had severe, protracted bouts of diarrhea (P6, P7 and P8) temporarily requiring parenteral nutrition. P7 developed chronic cholestasis and sub-occlusion, requiring treatment by jejunostomy. Another patient presented nodular gastritis and colon stenosis associated with an infiltration of $CD3^+$ lymphocytes (P8). Finally, a gastroesophageal reflux was detected in four patients (P3, P4, P8 and P9). Five patients presented developmental delay. Four of these patients presented a slight cognitive and motor developmental delay in the first few years of life, but they subsequently displayed age-appropriate development and attended ordinary schools (Table 1). Only P4, who carries mutations of *ZBTB24*, displayed marked mental retardation requiring attendance at a specialized institution. Four of the patients in this series (P3, P4, P6 and P8) were highly sensitive or aggressive impairing the interpersonal relationship, notably the interactions with the healthcare team. Such symptoms may affect the patient care and the follow-up.

Infections

Infections, mostly respiratory infections (recurrent otitis, bronchitis) were a prominent clinical feature in eight patients, and three patients had bronchiectasis (Table 2). P9, the sister of P1, developed no infections, owing to early diagnosis [54], leading to early intravenous immunoglobulin (IVIgG) replacement. Diverse pathogens were responsible for the infections observed in these patients: bacteria (encapsulated or not, Table 2), viruses, fungi and parasites (Table 3).

Autoimmune and Immune-Mediated Manifestations in ICF1 Patients

Two patients (P3 and 8) with *DNMT3B* mutations developed severe autoimmune signs. P3 developed autoimmune hepatitis with high levels of alkaline phosphatase and gamma-glutamyl-transferase in the serum, but without detectable autoantibodies at the age of 12 years. Liver biopsy revealed a significant infiltration of the portal area by inflammatory cells, including a few macrophages and $CD8^+$ T cells, in particular. Strikingly, flare-ups of the disease were marked by an increase

Table 1 Clinical and genetic data for the French ICF patients

Patient	Sex	Origin	Year of birth	Consanguinity	First clinical sign (age)	Diagnosis (age)	Mutation	Facial anomalies	Gastro-intestinal signs	ENT infections	AI manifestations	Mental retardation	Treatment	Progression
ICF1							*DNMT3B*							
P1	F	Gambia	2009	Yes	1 m	10 m	c.1747G > A	+	−	+	−	−	IVIG + CTX + AP	4 y. Stable
P2	F	Reunion	2010	No	2.5 m	11 m	c.1964C > T/c.143-22delC and c.1252 + 13 T > G	−	−	+	−	−	IVIG + CTX	
P3	M	France	1996	Yes	3 m	9.5 y	c.2324C > T	+	+	+	+	−	IVIG + CTX + IS	18 y. Infections and hepatitis
P5	M	French West Indies	2008	No	6 m	9 m	c.310C > T/c.2162 T > C	+	−	+	−	−	IVIG + CTX + AP	
P7	M	France	1985	No	3 m	11.5 y	1 bp ins codon 53/c.2302 + 139G > A and c.2302-212 T > C and c.2421-91G > A	+	++	+	−	−	IVIG + CTX + AP	Died 16 y, respiratory failure
P8	F	Morocco	1991	Yes	2 m	8 m	c.2450 A > G	+	++	+	+	−	HSCT	Died 22 y, 5 y after HSCT
P9	F	Gambia	2013	Yes	4 m	1 m	c.1747G > A	+	+	−	−	−	IgGIV	8 m. Stable
ICF2							*ZBTB24*							
P4	F	Cape Verde	1996	No	12 m	11.75 y	c.787 A > T/980_981delGT	−	+	+	−	+	IVIG + CTX+ Zx	18 y. Stable
ICF3							*CDCA7*							
P6	F	France	1978	Yes	6 m	11 y	c.911G > A	−	+	+	−		IVIG + CTX	Lost to follow-up

AI autoimmune, *AP* antibiotic prophylaxis including oral penicillin, macrolides and/or cephalosporin, *CTX* otrimoxazole, *ENT* ear-nose-throat, *IS* immunosupressive treatment, *IVIG* intravenous immunoglobulins, *m* months, *y* years, *Zx* azythromycin. P9 is the younger sister of P1. Thanks to early diagnosis, she did not develop ENT infections

Table 2 Bacterial infections in the French cohort of ICF patients

Patient	T-cell immunity	IgG (g/l)	Age at the first infection (months)	ENT infections	Complications of respiratory infections	Pneumonia	Bacteria detected	Sepsis	Bacteria detected	Meningitis	Bacteria detected
ICF1											
P1	+/− ↘	2.9	1	+		3	*P. aeruginosa*, *S. pneumoniae*				
P2	N	1.3	2.5	+		1	*P. aeruginosa*	2	*P. aeruginosa*		
P3	↘	3.79	43	+		1					
P5	N	0.57	6	+		1	*E. coli*	1	*E. coli*		
P7	↘	2.82	5	+	Bronchiectasis	1					
P8	+/− ↘	0.06	2	+	Bronchiectasis	2				1	*S. pneumoniae*
P9	+/− ↘	2.87		–		0					
ICF2											
P4	+/− ↘	8.15	12	+	Bronchiectasis Lobectomy	2	*S. pneumoniae*				
ICF3											
P6	N	2.5	6	+		1				1	*H. influenzae*

N normal, *ENT* ear-nose-throat

in levels of $CD8^+CD45RA^-CCR7^-$ effector memory T cells in the peripheral blood. Since the age of 14 years, this patient has received immunosuppressive therapy combining tacrolimus and corticosteroids, followed by anti-CTLA4 agents and corticosteroids, leading to a partial control of hepatitis. He developed progressive renal failure at age 19. Renal biopsy showed massive interstitial infiltration by lymphocytes with the same phenotype as the liver infiltrate. At time of writing, P3 was undergoing pulsed steroids. Recently, such autoimmune phenomena were reported in an ICF2 patient [51]. P8 developed autoimmune thyroiditis with anti-thyroid peroxidase antibodies, at the age of 16 years. Of note, this patient showed other immune-mediated diseases as idiopathic psoriasis. She had psoriatic lesions at the age of 4 years and was initially treated with topical corticosteroids and then with retinoids, with a favorable outcome. This patient also displayed arthritis associated with synovitis. Neutrophils were abundant in the sterile synovial fluid and a synovial biopsy showed inflammatory lesions. The patient was treated with oral anti-inflammatory drugs, intra-articular steroids and a higher dose of IVIG, with beneficial effects. A non-septic arthritis has already been reported in ICF patient [22]. Finally, P8 experienced chronic anemia associated with thrombopenia, partially due to nodular regenerative hyperplasia. Because no other underlying cause was detected, including bone marrow investigations, these cytopenia have been linked to immune disorders.

Immunological and Hematological Investigations

We analyzed the peripheral blood B-cell populations of the nine patients. B-cell immunity was severely impaired in all patients, with an absence of $CD27^+$ memory B cells (0.2 to 1 % of total B cells), contrasting with normal numbers of circulating B lymphocytes (Table 5, normal ranges from [55]). B-cell defects have been associated with hypogammaglobulinemia in ICF patients [2]. We therefore investigated B-cell function in vitro (n = 5, Table 4). B cells from all ICF1 patients tested showed a weak response to CD40 activation or no response at all, and an absence of Ig class-switch recombination. These features were not found in the ICF2 patient. Consistent with these findings, serum Ig levels were low for age in all ICF1 patients, whereas IgG levels were almost normal in the ICF2 patient. We assessed the production of immunoglobulins in vivo, by testing for antibodies against protein antigens after regular immunization (n = 5, Table 4). All of the patients displayed an absence of specific antibodies against recall antigens (Table 4).

$CD4^+$ and $CD8^+$ T-cell counts and percentage were normal in all but three of the patients (P3, P7 and P9; Table 5). Naive $CD45RA^+CD31^+CD4^+$ T-cell counts were low in all patients, whereas naive $CD8^+$ T-cell counts were normal in all but one patient (P3). T-cell function was assessed in vitro for eight patients. In all but one of these patients (P7), normal T-cell

Table 3 Viral and fungal infections in French ICF patients

Patient	Viral infection		Age	Fungal infection	Age	Other infection	Age
ICF1							
P1	+	CMV systemic infection	4 y	−			
P2	+	Parvovirus B19 erythroblastopenia	6 m	−			
P3	+	Severe chicken pox[a]	5 y	−			
		Herpes zoster	13 y				
P5	+	Disseminated adenovirus	6 m	−		*Pneumocystis jirovecii* pneumonia	7 m
P7	−			+ Candidiasis	18 m		
P8	+	Influenza virus		+ Candidiasis	7 m, 14 y	Giardiasis	6 y
P9	−			−			
ICF2							
P4	+	Severe mononucleosis	3 y	+ Candidiasis	1 y		
ICF3							
P6	+	Influenza virus	6 m	−			

[a] *S. aureus* superinfected the skin lesions of P3 after chicken pox

proliferation was observed in response to phytohemagglutinin (PHA) stimulation. By contrast, six patients displayed low levels of T-cell proliferation in response to antigens such as candidin and tetanus toxoid (P1, 3, 4, 5, 7 and 8).

Treatment and Outcome

All patients had been on polyvalent IgG replacement therapy since a mean age of 5 years (range: 3 months to 15 years) and antibacterial prophylaxis since a mean age of 4.1 years (range: 3 months to 11 years, Table 1). Prophylaxis greatly decreased the incidence of ENT and systemic infections, indeed only two systemic infections occurred in patients on IgG substitution: one case of sepsis (P2) and one of systemic CMV infection (P1) treated with ganciclovir. Attempts to decrease the dose of preventive treatment systematically resulted in a recurrence of ENT infections. For instance, P7 developed pneumonia when the interval between IgG infusions was increased. Physiotherapy helped to attenuate respiratory symptoms in two patients. All the ICF1 patients required iron supplementation due to iron-deficiency anemia. Such supplementation was not required for the ICF2 patient.

In this series, P8 was the only patient to undergo HSCT, to treat severe cytopenia and autoimmune signs. She received stem cells from a related HLA-matched donor at the age of 17, after conditioning with alemtuzumab, fludarabine and melphalan. Cyclosporine treatment was administered to prevent graft-versus-host-disease. Three months after HSCT, the rate of donor chimerism was almost 97 %, and IVIgG treatment was stopped 1 year later. However, severe refractory psoriasis recurred 2 years after HSCT, necessitating anti-TNF therapy; pancytopenia persisted (1160/mm^3 neutrophils, 11 g/dl hemoglobin, 14,000/mm^3 platelets). P8 died, of unknown causes, at the age of 22 years, 6 years after HSCT.

Discussion

We provide here a detailed description of the genetic, clinical and immunological features and outcomes of nine patients with ICF syndrome followed in France. We identified six previously unknown mutations of *DNMT3B*, all of which were predicted to decrease its methyltransferase activity. In mice, *Dnmt3b* knockout is lethal early in embryonic development [56], whereas hypomorphic mutations similar to those found in ICF1 patients lead to developmental defects at later stages [4, 57]. Consistent with these data, the only nonsense mutation identified here (c.310C > T) was heterozygous, as already reported for other ICF1 patients [19, 21, 35]. By contrast, most ICF2 patients harbor nonsense mutations. No relevant genotype-phenotype association could be established in ICF1 patients, but missense mutations in ICF2 patients were found to be correlated with higher serum Ig levels and lower frequencies of infection [15, 27]. Several clinical features also differed between ICF1 and ICF2 patients. First, the ICF1 patients tended to be diagnosed earlier than the ICF2 patients, probably due to the higher incidence of infections and slightly more severe hypogammaglobulinemia in ICF1 than in ICF2 patients. The roles of DNMT3B and ZBTB24 in antibody production have not yet been investigated in vivo.

Second, ICF2 patients suffer from more severe mental retardation than ICF1 patients: in our series, only the ICF2 patient required education at a specialized institution, and all but one of the other ICF2 patients reviewed displayed mild or severe mental retardation, whereas almost 70 % of the ICF1

Table 4 B-cell exploration in French ICF patients

Age	P1 1.5 y	P2 8 m	P3 5 y	P4 11 y	P5 6 m	P6 10 y	P7 16 m	P8 6 m	P9 2m
AN CD19+	**689** (*1600–3700*)	**640** (*1300–6300*)	250 (*180-1300*)	286 (*250–410*)	**308** (*1300–6300*)		**322** (*1600-3700*)	**885** (*1300-6300*)	512 (*300–2000*)
%CD19+ CD27+	**2.6** (*7,5–10,9*)	**1.3** (*4,3–8,3*)	**1** (*11,1–20,4*)	**2** (*11,8–25,4*)	**1** (*4,3–8,3*)			**0.2** (*4,3–8,3*)	**<1%** (*2,9–4,5*)
%IgD+ IgM+	39		0	67.4	99				
% IgD- IgM+	10			8.5					
%IgD- IgM-	36			15					
In vitro class Ig switching	Defect	Defect	Defect	N	Defect				
IgG (g/l)	**2.9** (*4,82–8,96*)	**1.3** (*3,35–6,23*)	3.79 (*5,49–10,19*)	8.15 (*6,55–12,29*)	**0.57** (*3,35–6,23*)	**2.5** (*6,55–12,29*)	**2.82** (*4,82–8,96*)	**0.06** (*3,35–6,23*)	**2,87** (*2,95–5,49*)
IgA (g/l)	**<0.04** (*0,33–1,22*)	**0.21** (*0,27–0,86*)	<0.06 (*0,41–1,41*)	1.28 (*0,5–2,03*)	**<0.06** (*3,35–6,23*)	**0.1** (*0,5–2,03*)	**0.2** (*0,33–1,22*)	**0.06** (*3,35–6,23*)	**<0,05** (*0,12–0,38*)
IgM (g/l)	**0.67** (*0,5–1,53*)	**<0.1** (*0,48–1,36*)	<0.06 (*0,54–1,53*)	**0.18** (*0,53–1,62*)	**<0.04** (*3,35–6,23*)	**0.4** (*0,53–1,62*)	**<0.04** (*0,5–1,53*)	**0.06** (*3,35–6,23*)	**<0,05** (*0,3–0,85*)
Vaccine-specific serologies									
Tetanus	**<N**		**<N**	**< N**			**<N**		
Diphtheria	**<N**			**< N**	**<N**				
Poliovirus			**< N**	**< N**			**<N**		
Pneumococcus				**< N**					
Allohemaglutinins A/B				**< N**				**<N**	
B cell proliferations									
IL-4	↘	↘	↘		↘				
CD40 + IL-4	↘	↘	↘	N	↘				

The absolute numbers of lymphocytes per μl blood are shown for each subpopulation. The numbers in brackets indicate normal values for age and the bold numbers indicate values outside the normal age. P6 had 10% B cells but absolute counts were not given. P7 had normal total B-cell counts, but $CD27^{+}$ memory B cells were not evaluated. N: normal. Empty boxes indicate that the data concerned were not available

patients were of normal intelligence. ZBTB transcription factors have been implicated in the differentiation of the hippocampal neurons playing a key role in cognition and memory [58, 59]. Studies of the contribution of ZBTB24 to neurogenesis may improve our understanding of the neurological signs in ICF2 patients.

We report here, for the first time, the occurrence of autoimmune and immune-mediated signs in ICF1 patients outside the context of HSCT [60] or granulomatous phenomena [51]. Consistent with these findings, longer CDR3 domains harboring larger numbers of positive charges, which have been associated with autoreactivity and autoimmune diseases, were found in ICF1 patients [2, 61–64]. This observation suggested that clonal deletion might be defective in ICF patients, leading to autoimmune signs [2]. However, B cells do not seem to play such a prominent role in ICF autoimmunity. First, autoimmunity appears to be uncommon in ICF syndrome, whereas B-cell deficiency is frequent in the various cohorts of ICF patients. Second, in our study, autoimmune hepatitis was linked to T-cell disorders with an absence of antibody detection, highlighting a possible role of cellular immunity. T-cells seem also involved in autoimmune signs previously reported in one ICF2 patient. Indeed, periportal CD8+ T-cells infiltrates were observed in repeated liver biopsies [51]. Autoimmune manifestations and inflammatory disorders in both ICF1 and ICF2 patients could reflect a break of T-cell tolerance or defects in regulatory T-cell populations [65, 66].

Our study also confirmed the absence of $CD19^{+}CD27^{+}$ memory B cells in ICF1 and ICF2 patients. The lack of long-lived memory B cells and plasma cells may result from a terminal B-cell differentiation block, activation or a survival defect in long-lived memory B cells. CD27 is widely associated with B-cell activation and differentiation, and low levels of *CD27* expression, due to methylation defects, have been found in ICF lymphoblasts [11, 67–69]. The propensity of ICF B cells to undergo apoptosis in vitro *is* consistent with the hypothesis of a survival defect [2]. Moreover, it has been shown that the *DNMT3B* mutations underlying ICF lead to the apoptosis of murine thymocytes [4]. However, a deficiency of $CD19^{+}CD27^{+}$ memory B cells does not mean a total absence of memory B cells. It remains unknown whether $CD27^{-}$ memory B cells are present in ICF patients, but such cells have been identified in normal and pathological circumstances [70, 71].

We have described the therapeutic strategies and follow-up of the French ICF cohort. All patients received IgG substitution, which helped to decrease the rate of ENT and pulmonary infections. Indeed, IgG replacement is the mainstay for the treatment of antibody deficiencies [72]. In litterature, 18 ICF patients were reported to be on IgG treatment, and 16 of these patients experienced beneficial effects. ICF patients also presented an impairment of mucosal immunity, with low levels of IgA. Thus, IgG replacement does not prevent gastrointestinal

Table 5 T-cell exploration in French ICF patients

Age	P1 1.5 y	P2 8 m	P3 5 y	P4 11 y	P5 6 m	P6 10 y	P7 16 m	P8 6 m	P9 2 m
AN T lymphocytes	3498 (*700–8800*)	2336 (*1400–11,500*)	1133 (*850–4300*)	1738 (*1200–2600*)	1650 (*1400–11,500*)		506 (*700–8800*)	4956 (*1400–11,500*)	2432 (*2500–5500*)
AN CD4	2226 (*400–7200*)	1440 (*1000–7200*)	**177** (*500–2700*)	836 (*650–1500*)	1034 (*1000–7200*)		**69** (*400–7200*)	3245 (*1000–7200*)	1952 (*1600–4000*)
AN CD8	954 (*200–2800*)	672 (*200–5400*)	942 (*200–1800*)	858 (*270–860*)	594 (*200–5400*)		414 (*200–2800*)	1239 (*200–5400*)	**384** (*560–1700*)
% naive CD4	49 (*56–96*)	50 (*77–97*)	26 (*52–92*)	23 (*58–70*)	40 (*77–97*)				
% naive CD8	46 (*10–100*)	75 (*31–100*)	4 (*19–100*)	50 (*43–55*)	86 (*31–100*)				
Proliferations T									
PHA	N	N	N	N	N	N	↗	N	
OKT3			↗					N	
Tetanus	N	N	↗	N	↗	N	↗		
Candida	↗	N	↗	↗		N	↗	↗	
AN NK	1060 (*160–3700*)	160 (*68–3900*)	**44** (*61–510*)	**66** (*70–480*)	154 (*68–3900*)			235 (*68–3900*)	192 (*170–1100*)

AN absolute number, *N* normal, *ND* not determined, *PHA* phytohemagglutinin, *OKT3* anti-CD3. The absolute numbers of lymphocytes per μl blood are shown for each subpopulation. The numbers in brackets indicate normal values for age, whereas the numbers in bold indicate values outside the normal range

manifestations, such as diarrhea [72, 73]. Two patients in our cohort (P7 and P8) suffered persistent diarrhea. Antibiotic prophylaxis was used in addition to IVIgG, in eight of our patients. By contrast to the findings for our cohort, only five of the other ICF patients reviewed were reported to be on antibiotic prophylaxis. Notwithstanding the lack of detail provided in publications relating to previous cases, this difference highlights heterogeneity in patient care and the need for practical guidelines. The early initiation of Ig infusions totally prevented infections in P9. We therefore propose new molecular markers, to facilitate early diagnosis [52]. Five ICF patients (including one from our cohort) have undergone HSCT, which may be the last resort in terms of treatment options. Pancytopenia persisted in our patient, and two other patients developed autoimmune signs after HSCT [60]. As three patients recovered and achieved immune reconstitution, HSCT may be considered for patients with disease uncontrolled patients on IVIgG and antibiotic prophylaxis.

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