



## ORIGINAL PAPER

## Platelets, Thrombosis and Haemostasis

# Association of paediatric autoimmune cytopenia and inflammatory bowel disease suggests a common genetic origin

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## Funding information

Ministère de la Santé et de la Prévention; Association Bordelaise pour l'Avancement des Sciences Pédiatriques (ABASP); Association pour la Recherche et les Maladies Hématologiques de l'Enfant (RMHE); Association Française du Syndrome d'Evans (AFSE); O-CYTO

## Summary

The association of autoimmune cytopenia (AIC) and inflammatory bowel disease (IBD) has been reported in small series, but the incidence of and risk factors for IBD in children with AIC are not known. One thousand six hundred nine children with chronic immune thrombocytopenic purpura, autoimmune haemolytic anaemia or Evans syndrome from the prospective OBS'CEREVANCE cohort are included in this study. Overall, 15 children were diagnosed with IBD, including 14 who developed IBD after AIC diagnosis (median delay: 21 months). The only risk factor for IBD development is age at AIC over 10 years. Out of 10 children genetically tested, germline variants associated with autoimmune disorders were identified in three (*CTLA4*: two, *DOCK11*: one). In children and adolescents monitored for AIC or past history of AIC, especially children over 10 years, gastro-intestinal (GI) symptoms (recurrent abdominal pains, GI bleeding, chronic diarrhoea, weight loss) should suggest IBD and deserve specific work-up and genetic studies. Identification of a causal germline variant will allow targeted therapy.

M. Gilton and H. Fernandes contributed equally as first authors. N. Aladjidi and T. Leblanc contributed equally as the last authors.

Collaborators from the French Reference Center for Pediatric Autoimmune Cytopenia (CEREVANCE) and the French Pediatric Immunology and Hematology Society (SHIP) are provided in "Acknowledgements" section.

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## KEY WORDS

autoimmune cytopenia, children, inflammatory bowel disease, primary immunodeficiency

## INTRODUCTION

Immune thrombocytopenia (ITP), autoimmune haemolytic anaemia (AIHA), autoimmune neutropenia and Evans syndrome (ES) are rare diseases in children. Autoimmune cytopenia (AIC) may be associated with or reveal Inborn Errors of Immunity (IEI).<sup>1</sup> Inflammatory bowel diseases (IBD), Crohn disease (CD), ulcerative colitis (UC) and unclassified IBD are also rare in children and paediatric onset cases account for 10%–20% of all IBD patients.<sup>2</sup> Both AIC and IBD may be associated with other immunopathological manifestations (IM).<sup>3–6</sup> Simultaneous or sequential occurrence of AIC and IBD has only been reported in case reports or small retrospective series since 1970, mostly in adults, and comprehensive data on this rare association are scarce in children.<sup>7–11</sup> The aim of this study was to describe and analyse patients with paediatric onset AIC and IBD in the prospective OBS'CEREVANCE cohort.

## METHODS

Since 2004, children <18 years old with chronic ITP (cITP), AIHA and ES have been included in the national prospective OBS'CEREVANCE cohort and monitored lifelong.<sup>3–5</sup> CEREVANCE is the French national reference centre for childhood AIC. OBS'CEREVANCE is a prospective cohort (NCT05937828). The database is centralised in Bordeaux. Overall, 30 paediatric haematological centres, across the country contribute to the cohort under the coordination of three leading centres (Bordeaux, Paris-Trousseau and Paris-Robert-Debré). Long-term follow-up (F.U.) data are reported to CEREVANCE by adult centres to which patients have been transitioned. Written informed consent is obtained for all patients. Institutional Ethic Committee and the National Data Protection Authority approved the cohort study. ES is defined by any simultaneous (<1 month) or sequential bi or tri-autoimmune cytopenia. This database includes a complete description from birth to the last F.U.<sup>12</sup> Recorded IM include clinical IM and biological IM as defined in Table S1.<sup>5</sup> In this study, a patient with IM may have clinical IM, biological IM or both. Screening for clinical and biological IM is done annually or when a second-line therapy is discussed according to CEREVANCE guidelines. Hypogammaglobulinaemia is considered as transient when it occurs after rituximab and lasts less than 2 years. It is considered as long-lasting when over 2 years. Patients with ES were systematically offered genetic studies from 2015 (next-generation sequencing or whole-exome sequencing [WES]) and from 2019 are included in the ACTION study (NCT03912129). Other patients with AIC are genetically

screened in a real-life setting when IEI is suspected by treating physician. Variants are classified according to the American College of Medical Genetics (ACMG). Class 4 or 5 variants are regarded as causal and class 3 variants are considered only after functional validation. Our definition of IEI is based on the identification of a pathogenic variant or likely pathogenic variant.

All patients who had developed IBD during their F.U. were included in the present study. Data collection was stopped on 1 March 2023. IBD diagnosis was based on clinical symptom, radiology, endoscopy and pathology according to Porto criteria<sup>13</sup>; IBD activity indices were not available. All patients had at least one upper and lower endoscopy. Pathological reports were reviewed for all patients.

Regarding treatment, second-line treatments (SLTs) were treatment other than corticosteroids and intravenous immunoglobulins (IVIg) for AIC, and other than corticosteroids and mesalazine for IBD.

The independent effect of sex, age at AIC diagnosis, AIC type and associated IM was assessed in patients with IBD and in controls (patients with AIC and no IBD) through univariate and multivariate analysis by Cox regression. Controls were selected in the OBS'CEREVANCE database: Among 1594 patients, we excluded 700 patients with missing data or short F.U. We selected 894 patients with the same period of diagnosis and comparable F.U. Statistical analyses were performed using RStudio (V1.2.5033) and Prism (V9.1) software. A *p*-value <0.05 indicated statistical significance.

## RESULTS

Among 1594 patients included in the OBS'CEREVANCE cohort, 15 patients (10 males and 5 females) developed IBD, with cITP (*n*=9), AIHA (*n*=3) and ES (*n*=3) (Table 1). According to the AIC subtype, prevalences are as follows: 9/938 cITP (0.95%), 2/340 AIHA (0.6%) and 3/241 ES (1.25%).

In the IBD cohort, the median age at AIC diagnosis was 13 years (1–17) and the median F.U. from AIC diagnosis was 6.4 years (0.5–27.7). The median F.U. from IBD diagnosis was 3.7 years (0–15.4).

Eleven patients had received SLTs for AIC, with a median delay of 2 months (0–15) from diagnosis. At the last visit, AIC was in complete remission (CR) for 13 patients.

The median age at IBD diagnosis was 16 years (1–28). One patient was diagnosed with IBD 1 year before AIC. For the remaining patients, IBD occurred with a median delay of 21 months (0–179) after AIC. The timing of AIC and IBD diagnosis is given in Figure 1. Eleven patients had UC, three had CD and one had unclassified IBD. Of note, 14 of those patients had predominant colonic involvement. Overall, 14 patients had only lower gastro-intestinal (GI) involvement

TABLE 1 Patient characteristics.

Patient/sex	Familial anamnesis (first degree)	Age at AIC dg (year)	IBD	Age at IBD diagnosis (year)	Associated IM (number)	Type of IM [age at onset, years]		Second-line treatment		Status at last follow-up	
						IBD	Whole-exome sequencing (WES)	For AIC	For IBD	Age at last follow-up (years)	For AIC
UPN1/F	0	15	UC	16	1	ANA >1/160 [15 years]		0 AZA, INFL+		22	CR 6 years+ CR
UPN2/M	0	12	CD	23	6	Diabetes mellitus [3.0 years], eczema [13.0 years], HypoG after RTX and long-lasting [13.8 years], GLILD [19.3 years], HT [21.3 years], Biermer's disease [23.4 years], <b>CTLA4 variant exon 2 c.151C&gt;T; p.R51*</b>		RTX, AZA, ABA, SRL+ ABA+, IVIg		25	CR 3 years+ CR
UPN3/M	0	7	UIBD <sup>a</sup>	9	5	Asthma [3 years], GLILD [8.6 years], keratitis [9.7 years], ANA >1/160 [7 years], HypoG after RTX and long-lasting [8.4 years] <b>CTLA4 variant exon 2 c.410 C&gt;T; p.P137L</b>		RTX, ABA+ ABA+, IVIg		13	CR 6 years+ CR
UPN4 <sup>b</sup> /M	UC (father)	15	UC	15	0	Exome not conclusive		AZA, ELT, ROMI+ 0		19	CR 0.5 years+ PR
UPN5 <sup>b</sup> /M	CD (brother)	12	CD	17	2	ANA >1/160 [13 years], APS [15 years] Exome not conclusive		0 AZA+		18	CR 2 years+ CR
UPN6 <sup>b</sup> /M	0	2	UC	1	4	ANA >1/160, anti-thyroglobulin and anti-enterocyte antibodies [4 years] HypoG after RTX and long-lasting [3.0 years] <b>DOCK11 variant: c.3893 T&gt;G; p.Leu298Arg</b>		VBL, RTX, TCR, ROMI AZA, SRL, INFL, EVEROL Pheno-identical marrow transplantation, IVIg		15	CR 1 year+ CR
UPN7/F	0	13	UC	13	1	ANA >1/160 [14.8 years] Exome not conclusive		CSA INFL, GOL, AZA, VEDO, USTE, TOFA+		18	CR 1 year+ CR
UPN8/M	HT (mother) RA (father)	17	UC	17	2	Atopy [3 years], APS [17 years]		0 MESA+		18	CR 2 years NR
UPN9/F	0	15	UC	18	4	ANA >1/160, lowC4 [15.9 years], Sclerosis cholangitis [18.8 years], HypoG after RTX and transient [16 years]		RTX, CSA, CY, VCR, SPX AZA, ADA, INFL, MTX, VEDO, USTE, TOFA+		32	CR 16 years+ NR

(Continues)

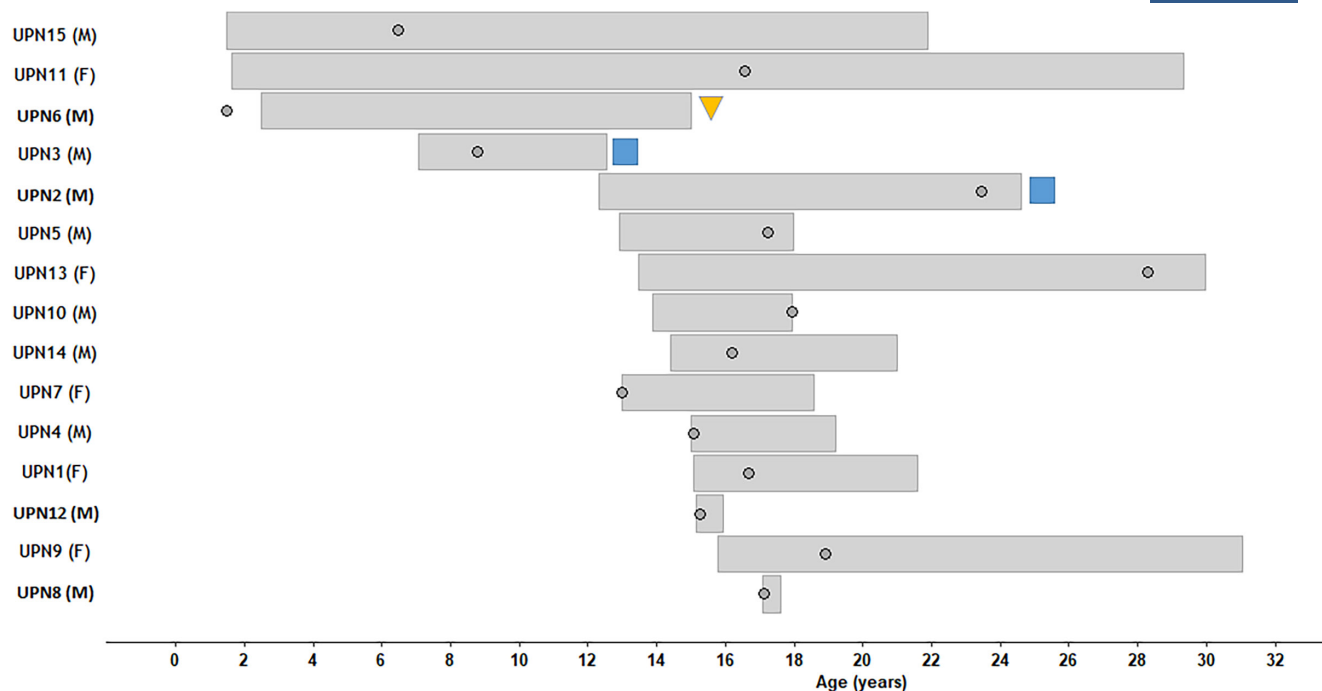
TABLE 1 (Continued)

Patient/sex	Familial anamnesis (first degree)	AIC	Age at AIC dg (year)	IBD	Age at IBD diagnosis (year)	Associated IM (number)	Type of IM [age at onset, years]		Second-line treatment		Status at last follow-up	
							Whole-exome sequencing (WES)	WES	For AIC	For IBD	Age at last follow-up (years)	For AIC
UPN10/M	0	AIHA	13	UC	17	2	Sclerosis cholangitis [17.9 years], pANCA [17 years]	MMF INFL, AZA, MESA+	MMF INFL, AZA, MESA+	18	CR 4 years NR	
UPN11 <sup>b</sup> /F	0	I TP	1	UC	16	2	HypoG unrelated to RTX [26 years], Biermer's disease [27.4 years] Exome not conclusive	0 MESA+	0 MESA+	29	PR PR	
UPN12/M	0	I TP	15	UC	15	3	HSP [4.0 years], ANA >1/160, anti-PR3 antibodies [15.2 years] Exome not conclusive	HCQ, ROMI 0	HCQ, ROMI 0	16	NR NR	
UPN13/F	HT (sister)	AIHA	13	UC	28	1	HypoG after RTX and transient [17.7 years] Exome not conclusive	CSA, MMF, RTX RTX+	CSA, MMF, RTX RTX+	30	CCR 1 year+ CR	
UPN14/M	APS (mother)	I TP	14	CD	16	2	Vascular acrosyndrome [15 years], APS [15.6 years]	VBL, ELT, DISUL, HCQ AZA, MESA+	VBL, ELT, DISUL, HCQ AZA, MESA+	21	CR 6 years CR	
UPN15/M	B-cell lymphoma (mother)	AIHA	1	UC	6	2	Giant cell hepatitis [1.6 years], HypoG after RTX and transient [2 years] Exome not conclusive	AZA, CSA, RTX AZA, MESA+	AZA, CSA, RTX AZA, MESA+	22	CR 5 years CR	

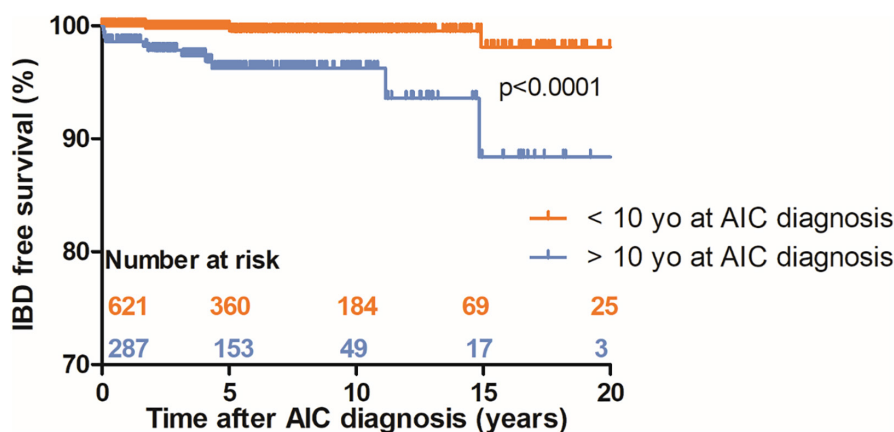
Abbreviations: 6 years+, continuous CR for 6 years but ongoing second-line treatment; ABA, abatacept; ADA, adalimumab; AIN, autoimmune neutropenia; ANA, anti-nuclear antibodies; APS, anti-phospholipid syndrome; AZA, azathioprine; CD, Crohn disease; CR, complete remission, no disease; CSA, cyclosporine; CY, cyclophosphamide; DISUL, disulone; ELT, eltrombopag; EVEROL, everolimus; GLILD, granulomatous lymphocytic interstitial lung disease; GOLJ, golimumab; HCQ, hydroxychloroquine; HSP, Henoch-Schönlein Purpura; HT, Hashimoto's thyroiditis; HypoG, hypogammaglobulinaemia; IBD, inflammatory bowel disease; IM, immunopathological manifestation; MESA, mesalazine; MME, mephenolate mofetil; MTX, methotrexate; NFL, infliximab; NR, no remission, active disease; pANCA, anti-neutrophil cytoplasmic antibodies; PR, partial remission; RA, rheumatoid arthritis; ROMI, romiplostim; RTX, rituximab; SPX, splenectomy; SRL, sirolimus; TCR, tacrolimus; TOFA, tofacitinib; UC, ulcerated colitis; UBD, unclassifiable IBD; USTE, ustekinumab; VBL, vinblastine; VCR, vincristine; VEDO, vedolizumab.

<sup>a</sup>The patient had chronic diarrhoea, loss of weight, elevated inflammatory parameters, elevated calprotectin, and had received a short pulse of corticosteroids shortly before endoscopy, that could have masked specific IBD aspects.

<sup>b</sup>Immunopathological history in second-degree relatives: Pt 4: CD, Pt 5: diabetes mellitus, Pt 6: UC, Pt 11: dysthyroidism.



**FIGURE 1** Clinical course of patients with timing for AIC and IBD diagnosis. Each horizontal band represents a single patient, from the age at diagnosis of AIC to the age at the last follow-up. The grey dot represents the age at diagnosis of IBD. Patient with *CTLA4* variants are marked with a blue square (UPN2 and UPN3); the patient with a *DOCK11* variant is marked with an orange triangle (UPN6). AIC, autoimmune cytopenia; IBD, inflammatory bowel disease.



**FIGURE 2** IBD-free survival curve in children diagnosed with AIC, according to the age of AIC diagnosis. AIC, autoimmune cytopenia; IBD, inflammatory bowel disease.

and one patient (UPN4) with UC also presented with non-specific/non-*Helicobacter pylori* gastritis at initial evaluation. Overall, pathological findings were classical. At the last visit, six patients still had active IBD.

Five patients were diagnosed with IBD while on treatment: three were on ongoing corticosteroids (UPN4, 7, 15), one was on corticosteroids and IVIg (UPN12) and one was on hydroxychloroquine (UPN14). Two patients had received prior SLT for AIC. Eleven patients received one to seven SLTs for IBD, with a median delay of 5 months (0–154) from IBD diagnosis. Of note, the proportion of patients receiving second-line therapies in the control group was 50% as reported before.<sup>14</sup>

Fourteen patients presented one to six other associated IM, before AIC diagnosis for two (UPN2, 12) and up to 25 years after AIC for other patients. None of those 15 patients presented with non-clonal nor malignant lymphoproliferation. Seven patients developed hypogammaglobulinaemia, and three were still on IVIg replacement at the last F.U. No patient had severe, recurrent or opportunistic infections.

Ten out of 15 patients had WES. Germline variants in genes associated with IEI were identified in three patients: *CTLA-4* (UPN2, 3) and *DOCK11* (UPN6). These three variants were reported as pathogenic in previous publications.<sup>15,16</sup> The two patients with *CTLA4* variant were

treated with abatacept and had a good clinical outcome for both AIC and IBD (Table 1). For patients without underlying genetic diagnosis, exome data are regularly reanalysed, as new pathogenic pathways for autoimmunity are newly described.

The analysis of the 14 patients who developed IBD post-AIC diagnosis, and the 894 controls showed that only age over 10 years at AIC diagnosis was significantly associated with IBD occurrence (Hazard ratio: 14.95, 95% confidence intervals: 3.32–67.2,  $p$ : 0.004) (Figure 2). Sex ( $p$ : 0.303), AIC type ( $p$ : 0.23) and history of associated IM ( $p$ : 0.496) were not significantly associated with IBD (Table S2).

## DISCUSSION

Identification of immune disorders is an important concern for haematologists. This comprehensive national long-term unbiased analysis of the haematological paediatric cohort demonstrates that children with AIC have an increased risk of developing IBD if they are older than 10 years at diagnosis. Among 1594 patients included in the OBSCEREVANCE cohort, 15 had IBD, giving a prevalence of 0.9%. IBD prevalence in Western European paediatric population is estimated to be 58.9–66.3/100 000.<sup>17</sup> Using this estimation, the number of expected cases in our cohort would be around one case only (0.94–1.06). Moreover, we cannot exclude that some patients with IBD at a younger age who later develop AIC could be missed, as they are predominantly followed by gastroenterologists.

Chronic ITP was the main AIC represented in this subgroup as described in previous reports in children and adults. In this study, 12 out of 15 patients have cITP, isolated or part of ES.<sup>10</sup> Nevertheless, IBD remains a very rare event in cITP (1% in our cohort) as reported before by our group.<sup>18</sup>

As reported in our previous long-term study of ES patients, the outcome of those patients is ultimately more impacted by IBD and other IM than by AIC itself and most of the patients were in haematological CR at the last visit.<sup>5</sup> In fact, a significant proportion of the cohort had multiple IM, hypogammaglobulinaemia and several second-line immunosuppressive treatments.

Regarding IBD presentation, a striking point is the UC type predominance (11/15) and colonic involvement, as in other series,<sup>10,11,16,19</sup> whereas CD is usually more frequent in children. This predominance of UC in children with AIC deserves to be validated by further studies.

Of note, hypogammaglobulinaemia was associated with rituximab in seven out of 15 patients and was classified as transient in four cases (UPN9, 11, 13, 15). IT was long-lasting and symptomatic in three in whom it was associated with underlying IEI (UPN2, 3, 11). Secondary long-lasting hypogammaglobulinaemia after rituximab in children with autoimmune diseases is well reported. It must be seen as a marker of underlying IEI and lead to genetic studies.<sup>20,21</sup> Patients with hypogammaglobulinaemia have a high prevalence of lower GI manifestations.<sup>22</sup> IBD are known to result

from a complex interaction between environmental and immune factors, likely mediated by the impact of environmental exposures on the intestinal microbiome in genetically susceptible individual.<sup>23</sup> The benefit of immunoglobulins replacement to prevent infections has been established in patients with common variable deficiency<sup>24</sup> and it has also been suggested that IVIg replacement may prevent IBD progression in patients with X-linked agammaglobulinaemia.<sup>25</sup> Its benefit to prevent IBD in this very context of AIC remains to be established.

In the present study, six out of 15 have IM in first-degree relatives and 14 out of 15 patients have other IM including hypogammaglobulinaemia. Overall, these features and the combination of AIC and IBD in our patients are suggestive of an underlying genetic condition. Germline pathogenic variants were identified in three of those patients. The proportion of informative genetic tests is only 30% in this study. This low proportion may be due to the fact that we report only on pathological or likely pathological variants. We cannot exclude that some variants classified as non-significant may actually be causal. Alternatively, genes may be inactivated through other mechanisms that change in the sequence. In previous studies from our group,<sup>3–5</sup> AIC was often the first symptom of immune dysregulation and IEI was identified in 40% of 80 patients with paediatric-onset ES. In fact, AIC and GI manifestations such as IBD are the two main features of immune dysregulation known to be associated with IEI. They are reported, respectively, in 31.4% and 24.4% of 2183 patients with IEI from the French database patients and the risk of AIC and IBD are estimated to be, respectively, at least 120 times and 80 times higher than in the general population.<sup>26</sup>

The patient with DOCK11 deficiency (UPN6) was recently reported: In this new X-linked actinopathy associated with early onset autoimmunity, ITP was described in four out of eight patients and GI manifestations in four out of eight patients.<sup>15</sup> Of note, a germline variant may suggest early autoimmunity onset and severe disease, as reported in a recent survey of patients affected by activated phosphoinositide 3-kinase delta syndrome, another syndrome associated with cytopenia and enteropathy. In our cohort, age at AIC and IBD diagnosis is actually younger for the DOCK11 patient, a syndrome known to be associated with overall early and severe autoimmunity.<sup>15</sup> This is not the case for patients with *CTLA4* variants (Table 1). It is likely that time of onset and autoimmunity severity are linked to the involved defect. Additionally, for one defined disease, the phenotype is often very heterogeneous and may also vary with the type of variant as reported for *CTLA4* syndrome in which enteropathy is more frequent in patients with a missense mutation than in patients with nonsense or insertion/deletion frameshift mutations.<sup>16</sup>

Of note, there is a growing number of genes associated with various IM including IBD and with monogenic IBD.<sup>16,27,28</sup> More studies are needed to define the full landscape of associations between AIC and IBD or other IM and the clinical benefit associated with early identification of germline variants.

The small number of patients and the heterogeneity of treatments given preclude any analysis on the benefit associated with one or another second-line therapy or on the impact of AIC control on IBD outcomes. At the last F.U., AIC was in CR for 13 out of 15 patients, five with ongoing treatments also used for IBD. In a French study of 40 adults with AIC and IBD, 25 patients had cITP. Ciclosporin and anti-Tumor-Necrosis-Factor tended to be efficient on both diseases.<sup>10</sup> However, it is difficult to compare the series of adults and children. Moreover, one should also consider the different referral pathways: local or national level and predominance of haematology or gastroenterology centres.

The identification of germline pathogenic variants clearly may prompt targeted therapy, as illustrated in a recent study from our group: in CTLA4 pathway defect abatacept allowed a favourable outcome of AIC and other IM including IBD (Table 1, UPN2, 3).<sup>29</sup> Lastly, in a case-by-case discussion, haematopoietic stem cell transplantation could also be considered in patients with germline variants and severe disease, as in our patients with DOCK11 deficiency.

In conclusion, a multidisciplinary approach is warranted in children with AIC, especially when they are older than 10 years at initial diagnosis.

In children and adolescents being monitored for AIC or past history of AIC, especially children diagnosed with AIC over the age of 10 years, GI symptoms (recurrent abdominal pains, GI bleeding, chronic diarrhoea and weight loss) should suggest IBD and lead to a specific work-up including inflammatory markers and calprotectin, established screening test for bowel inflammation,<sup>30</sup> in order to establish an indication for endoscopy. Optimally, early identification of monogenic underlying disease will allow personalized patient care.

## AUTHOR CONTRIBUTIONS

**M. Gilton:** Investigation; formal analysis; writing – original draft; review and editing. **H. Fernandes:** Investigation; formal analysis; review and editing. **C. Martinez:** Investigation; formal analysis; writing – original draft; review and editing. **G. Leverger:** Investigation; formal analysis; review and editing. **W. Abou Chahla:** Investigation; formal analysis; writing – original draft; review and editing. **V. Li Thiao Te:** Investigation; formal analysis; writing – original draft; review and editing. **M. Deparis:** Investigation; formal analysis; writing – original draft; review and editing. **C. Armari Alla:** Investigation; formal analysis; writing – original draft; review and editing. **N. Garnier:** Investigation; formal analysis; writing – original draft; review and editing. **J. Benadiba:** Investigation; formal analysis; writing – original draft; review and editing. **A. Marie-Cardine:** Investigation; formal analysis; writing – original draft; review and editing. **F. Rieux-Laucat:** Investigation; formal analysis; writing – original draft; review and editing. **C. Picard:** Investigation; formal analysis; writing – original draft; review and editing. **N. Aladjidi:** Conceptualization; methodology investigation; supervision; formal analysis; writing – original draft; writing

– review and editing; **T. Leblanc:** Conceptualization; methodology investigation; supervision; formal analysis; writing – original draft; writing – review and editing.

## ACKNOWLEDGEMENTS

The authors thank the patients, their families and the medical and paramedical teams involved in the CEREVANCE prospective cohort study since 2004. We thank the following paediatricians who are investigators of the OBS'CEREVANCE study: Sébastien Heritier (APHP—Trousseau), Mony Fahd (APHP—Robert Debré), Marlène Pasquet (Toulouse), Caroline Thomas (Nantes), Vincent Barlogis (Marseille), Eric Jeziorski (Montpellier), Sophie Bayart (Rennes), Pascal Chastagner (Nancy), Nathalie Cheikh (Besançon), Corinne Guitton (APHP—Bicêtre), Catherine Paillard (Strasbourg), Julien Lejeune (Tours), Frédéric Millot (Poitiers), Isabelle Pellier (Angers), Martin Castelle (APHP—Necker), Liana Carausu (Brest), Christophe Piguet (Limoges), Claire Pluchart (Reims), Jean-Louis Stephan (Saint Etienne), Claire Briandet (Dijon) and Eric Doré (Clermont Ferrand). We also thank Françoise Mechinaud for the review of English.

## FUNDING INFORMATION

The OBS'CEREVANCE cohort was supported since 2004 by the French Ministry of Health (Programme Hospitalier de Recherche Clinique [PHRC] 2005, Rare Disease Plan 2007, 2017, 2023), the Association Bordelaise pour l'Avancement des Sciences Pédiatriques (ABASP) research charity, the Association pour la Recherche et les Maladies Hématologiques de l'Enfant (RMHE) research charity, the Association Française du Syndrome d'Evans (AFSE) and the O-CYTO patients' association.

## CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to disclose.

## DATA AVAILABILITY STATEMENT

For original data, contact [thierry.leblanc@aphp.fr](mailto:thierry.leblanc@aphp.fr).

## ETHICS STATEMENT

The cohort study was approved by the institutional ethics committee, and the database was registered with the data protection authority (CNIL, 1396823 V1).

## PATIENT CONSENT STATEMENT

Written informed consent was obtained from the patients themselves, when adults, or from the parents/guardians of minors for inclusion in the OBS'CEREVANCE cohort.

## CLINICAL TRIAL REGISTRATION

The OBS'CEREVANCE cohort is registered on ClinicalTrials (NCT03912129).

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Gilton M, Fernandes H, Martinez C, Leverger G, Abou Chahla W, Li Thiao Te V, et al. Association of paediatric autoimmune cytopenia and inflammatory bowel disease suggests a common genetic origin. *Br J Haematol*. 2024;00:1–8. <https://doi.org/10.1111/bjh.19701>