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Alimentary Tract

Intractable diarrhea in infancy and molecular analysis: We are beyond the tip of the iceberg

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ABSTRACT

Background: Intractable diarrhea (ID) could be defined as a syndrome of severe chronic diarrhea associated with malnutrition not easily resolved by conventional management.
Aims: To provide an overview on etiology and management of ID patients in Italy in the last 12 years.
Methods: The members of Italian Society for Pediatric Gastroenterology, Hepatology and Nutrition (SIGENP) enrolled all ID patients seen between January 1, 2011 and December 31, 2022.
Results: 69 children were enrolled (49 M, 20 F; median age at ID onset 9.5 days) from 7 tertiary care pediatric centers. Overall 62 patients had genetic diseases; 3 had infantile Inflammatory Bowel Disease and 1 autoimmune enteropathy in absence of genetic mutations; 2 undefined ID. Defects of intestinal immune-related homeostasis caused ID in 29 patients (42 %).
Conclusion: ID is a rare but challenging problem, although the potential for diagnosis has improved over time. In particular, molecular analysis allowed to identity genetic defects in 90 % of patients and to detect new genetic mutations responsible for ID. Due to both the challenging diagnosis and the treatment for many of these diseases, the close relationship between immune system and digestive tract should require a close collaboration between pediatric immunologists and gastroenterologists, to optimize epidemiologic surveillance and management of ID.

1. Introduction

Intractable diarrhea (ID) was first described by Avery et al., in 1968 [1] as "a severe syndrome of chronic diarrhea"; Walker-Smith, in 1994 [2], re-defined intractable diarrhea of infancy as "a syndrome of severe chronic diarrhea associated with malnutrition which is not easily resolved by conventional management". In functional terms, ID causes Intestinal Failure (IF), that makes the gut unable to adequately digest and absorb food [3], thus making Parenteral Nutrition (PN) a life-saving strategy [4–8].

IF is characterized by a significant decrease in functional gut mass, falling below the threshold essential for the proper digestion and absorption of macronutrients, water, and electrolytes, crucial for optimal growth and development in children [9,10].

The use of central catheters for parental nutrition increased survival and patients with ID can reach adulthood. Indeed, the chance to start programs of home parenteral nutrition (HPN) allows hospital discharge of ID patients requiring long-term PN in the home care setting [11–21].

Across the years, definition of ID has evolved and has been supported previously from histology and presently from genomics, particularly from next-generation sequencing technology and whole -exome sequencing [22].

Indeed, in many forms of ID histological investigations may reveal abnormalities of the crypt-villous structure, enterocyte distribution, and morphology or inflammatory activity and may allow differential diagnosis. Molecular analysis detects genes causing the

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diseases and it provides an early and not invasive diagnostic tool to identify ID patients [5,6,8,23].

Overall new treatments, such as biologic drugs, hematopoietic stem cell transplantation (HSCT) and molecular analysis, that allows to early diagnose patients with ID due to gene mutations, have improved life expectancy and management of ID over time [24].

However, ID still appears as a heterogeneous syndrome with different etiologies but few data are available in literature updating the new therapeutic and diagnostic options. In particular since the first report form Avery et al. in 1968[1], who described some cases of infantile ID, in 1994 Ventura and coworkers published the results of the first Italian ID survey [25]; in 1998, Goulet and coworkers described the pathological findings of 47 cases of ID with persistent villous atrophy in early childhood ([26]; in 1999 Catassi et al. [12] reported prevalence and incidence of ID in Italy and finally in 2015 Hayriye and coworkers published a survey from Turkey that described the clinical picture of this heterogeneous group of diseases [4].

In consideration of the recent advance in this field, we design the present overview with the aim to update the spectrum of etiologies, outcomes and treatments of ID in the last 12 years in Italy, involving the members of the Italian Society of Pediatric Gastroenterology, Hepatology and Nutrition (SIGENP) from Italian tertiary care Centers of Pediatric Gastroenterology and Nutrition

2. Materials and methods

2.1. Study design

All SIGENP members were invited to participate in the present survey aiming to assess the prevalence of ID in Italy in 2022.

Cases recruited in this study included all patients followed since January 1, 2011 and December 31, 2022.

Patients fulfilling the following criteria were included: a)Age at ID onset 0 to 6 months; b) Diarrhea of more than 2 weeks' duration and c) Bowel rest and PN covering 100 % of the caloric intake for at least 1 week.

Exclusion criteria were: a) Infectious diseases; b) Proven infectious diseases in the last month before diarrhea onset in patient or family; c) ID with definitive or suspected diagnosis of short bowel syndrome or chronic intestinal pseudo-obstruction and d) Diarrhea which benefited from Enteral Nutrition (EN)

A database was shared among the members and the following data were asked: gender; Country of the origin; parental consanguinity; age at diarrhea onset; gestational age (GA); birth weight (BW), PN length (<3 months; 3–6 months or >6 months); dietary pattern before PN beginning; effects of fasting on diarrhea (persistence, total or partial disappearance); nutritional pattern (PN and dietary pattern), main treatment and current status at the last follow-up and the main diagnostic tool (molecular analysis, histological examinations or other).

2.2. Statistical analysis

Categorical variables were summarized as percentage, and continuous variables as median and range. Differences between ID categories were compared by Fisher exact test for categorical variables and by Mann-Whitney *U test* for continuous variables. Statistical evaluation and figures were generated using Graph Pad 6 for Windows.

2.3. Ethics

Written informed consent to participate in this study was provided by the participants' legal guardian. The study protocol has been approved by the Ethical Committee of Bambino Gesù Children Hospital in Rome. (Protocol Number 1382, October 7, 2021).

3. Results

Seventy-seven children with ID were enrolled in the study from 7 tertiary care pediatric centers for Gastroenterology and Nutrition (Bergamo, Firenze, Foggia, Genova, Napoli, Roma, Torino).

Eight cases were excluded because they did not fulfill inclusion criteria (two patients were older than 6 months at ID onset, 1 patient was affected by post enteritis syndrome, five children were affected by Food Protein-Induced Enterocolitis Syndrome (FPIES)).

Therefore, 69 children with ID were enrolled (49 male, 71 %; 29 female, 32 %; median age at disease onset: 9.5 days, range: 1–180 days).

Among all patients, 64 children were included in 3 main group based on the main mechanism of intestinal damage responsible for ID:

(a) Deficiency of nutrients/electrolytes transport;
(b) Structural and functional defects of absorption;
(c) Defects of intestinal immune-related homeostasis.

Additionally, 5 children showed ID due to undefined defects; in particular three of them had genetic profiles not due to known clinical pictures/pathophysiological mechanisms of ID.

Table 1 and Fig. 1 summarized the main features of each group.

Nineteen of 69 subjects (27.5 %) were already followed for a previously diagnosed ID at the study beginning; the remaining 50 (72.5 %) were newly diagnosed between 2011 and 2022. Fifty-nine patients (85.5 %), aged from 6 months to 34 years were alive at the last follow up.

In most children the onset was before 1 month of age (65 %).

Fig. 2 shows the age distribution at disease onset according to ID etiology.

3.1. Neonatal and family history

Complete neonatal data were available for 61 out of 69 patients: median BW was 2.880 Kg (range 1.250–4.100 kg) and median GA was 38 weeks (range 28–41 w). We did not observe significant differences in BW and GA among the 3 groups.

Parental consanguinity was reported in 11 of 69 subjects (16 %); it was highest in patients with deficiency of nutrients/electrolytes transport (25 %) and lowest in those with defects of intestinal immune-related homeostasis (10 %). Forty-nine patients (71 %) were Italian; the remaining 20 (29 %) came from other European Countries (9 %), from Asia (12 %) from Northern Africa (6 %) and from Southern America (1 %). Details about Country of origin are reported in *supplementary Fig. 1*.

3.2. Nutrition

Before starting PN patients were fed by the following formula: breast milk (63 %); standard infant formula (31 %); hydrolyzed formula (44 %) and amino-acids based formula (40 %). PN was started in all patients from 12 to 72 h from admission; fasting was maintained for at least one week after admission and caloric need was fulfilled by PN. Fig. 3 details the profile of diarrhea categorized as osmotic (disappearing at bowel rest); mixed (improving at bowel rest) and secretory (persisting at bowel rest) according to the group of intestinal damage. We found that secretory diarrhea was significantly associated with structural and functional defects of absorption ($p < 0.0001$); mixed diarrhea with defects of intestinal immune-related homeostasis ($p < 0.0010$) and osmotic

Table 1
Summary of the main features of the groups of diseases.

	N	M/F	G	BW	GA	Parental Cons.	Main treatments	Current status and age at the last FU (months)
Deficiency of nutrients/electrolytes transport	**8**	**6/2**		**2.9 (2.3–3.7)**	**39.5 (34–40)**	**2/8**		**8/8 Alive**
Glucose-galactose malabsorption	4	4/4	SLC5A1	3.l5 (2.9–3.79	40 (38–40)	0	GGFD	LLD (8 –114)
Congenital chloridrorrhea	2	1/1	SLC26A3	2.5 (2.3–2.7)	34 (34–34)	2/2	Salt supplementation + spironolattone	Salt supplement (32–60)
Abeta-hypobetalipoproteinemia	1	0/1	MTTP	3.2	40	0	LFDs + Vitamins+MCT	LFDs + Vitamins + MCT (13)
Anderson disease	1	1/0	SAR1B	2.3	39	0	LFDs + Vitamins + MCT	LFDs + Vitamins + MCT (133)
Structural and functional defects of absorption	**37**	**25/12**		**2.9 (1.2–3.8)**	**38 (28–39)**	**6/37**		**30/37 Alive**
Microvillus inclusion disease	11	7/4	MYO5B	2.7 (1.5–3.3)	36 (32–40)	2/11	HPN	10/11 Alive (HPN) (12–360)
Congenital tufting enteropathy	12	9/3	EPCAM (10) SPINT (2)	3.2 (2.0–4.0)	39 (33–41)	1/12	HPN	9/12 HPN 3/12 OD (2 SPINT) (26–363)
Tricho-hepatoenteric syndrome	5	2/3	TTC7A	1.9 (1.6.2.7)	35 (30–39)	1/5	HPN, Steroids, Immunosuppress HSCT, Biologics	4/5 Alive 2/4 OD; 2/4 HPN (82–411)
Congenital glycosylation defects	2	2/0	ALG6	3.6 (3.5–3.7)	37.5 (37–38)	0/2	PN + Low LCT	2/2 Exitus (10–32)
Proprotein convertase 1/3 deficiency	2	2/0	PCSK1	3.1 (3.1–3–1)	39 (39–39)	1/2	PN + Levothyroxine	2/2 OD (18–66)
Defects of intestinal immune-related homeostasis	**29**	**19/10**		**2.8 (2.2–3.2)**	**39 (37–41)**	**3/29**		**25/29 Alive**
Epithelial barrier dysfunction	6	5/1	NEMO (4) COL7A NOX1	2.8 (2.3–4.1)	38 (36–41)	1/6	Ig, PN, HSCT, Thiopurines, Anakinra, Steroids	5/6 Alive; 1HPN + Anakinra + Thiopurines 4 OD (18–154)
T and B lymphocytes defects	6	3/3	RAG1/2 JAK3 WAS ICF1	3 (2.2–3.6)	38.5 (38–41)	1/6	HSCT	5/6 Alive and on OD (13–69)
Defective T cell immune tolerance	1	1	FOXP3	2.5	37	0	HSCT	OD, free diet (144)
Hyperinflammatory diseases	5	5/0	HPS1 NLRC4 N-BAS CDC40LG STXBP2	3.2 (1.5–3.3)	37 (33–41)	1/5	Ig, PN, Anakinra, Steroids	4/6 Alive; 3 HPN; 1 OD +Steroids (12–118)
Immune dysregulation	2	2/0		2.6 (1.9–3.3)	38 (34–40)	1/2	PN, Thiopurines, Steroids, Mesalazine	OD, Steroids, Biologics, (24–81)
Infantile IBD *	3	2/1	NOD2	3.6 (3.3–3.7)	39.5 (39–40)	0	PN, Steroids, Immunos. Biologics	OD, Steroids, Biologics (18–23)
Autoimmune enteropathy	1	0/1	/	2.9	39	0	PN, Steroids, AA	OD, free diet (13)
Undefined defects	**5**	**3/2**		**2.8 (1.2–3.8)**	**34 (28–39)**	**1/5**		**3/5Alive**
Genetic profiles not clearly associated with ID	3	2/1	BRAF1 TSHR1 MT-Cyb	2.3 (1.2–3.3)	34.5 (28–38)	0/3	PN + Levothyroxine	1 Alive, on HPN (8–63)
Unknown etiology	2	1/1		3.0 (2.2–3.8)	33.5 (28–39)	1/2	PN	2/2 HPN (15–36)

BW: Birth weight; **GA:** Gestational age; **GGFD:** glucose galactose free diet, **LLD:** low lactose diet; **LFD:** low fat diet; **MCT:** medium chain tryglicerides; **HSCT:** hematopoietic stem cell transplantatio; **LCT:** long chain tryglicerides; **OD:** oral diet: **AA:** amino-acids based diet; **CMFD:** Cow's milk free diet; **PN:** parenteral nutrition; **HPN:** home parenteral nutrition; **ID:** Intractable diarrhea; **IBD**: Inflammatory Bowel Diseases.

Group A (8 pts)	Diagnosis
Gluc- galctose malabsorption (4)	SLC5A1 Mutations
Congenital chloridrorrea (2)	SLC26A3 Mutations
Abetaliproteinemia (1)	MTTP Mutation
Anderson disease (1)	SAR1B Mutation

Group B (32 pts)	Diagnosis
Microvillus inclusion disease (11)	MYO5B Mutations
Congenital tufting enteropathy (12)	EPCAM (10), SPINT (2) Mutations
Tricho-hepatoenteric syndrome (5)	TTC7A
Congenital defcts of glycosilation (2)	*ALG 6 Mutations*
Pro-protein convertase 1 deficiency (2)	PCSK1 Mutations

Prevalence of type of intestinal damage

Group C (24 pts)	Diagnosis (mutated genes/other)
Epitelial barrier dysfunction (6)	NEMO (4 pts), COL7A1, NOX1
T and B lymphocytes defects (6)	RAG1/2 (2 pts), JAK3 , WAS , ICF1, unknown gene
Defective T cell immune tolerance (1)	FOXP3
Hyperinflammatory diseases (5)	HPS1, NLRC4, N-BAS, CDC40LG, STXBP2
VEO-IBD with immunedysregulation (2)	NOD2
VEO IBD (3)	Histology suggestive for IBD
Autoimmune enteropathy (1)	Histology+autoimmunity

Group D (5 pts)	Diagnosis
Genetic profiles not clearly associated with ID (3)	BRAF1, TSHR 1, MT-Cyb Mutations
Unknown etiology (2)	Only clinical findings

Fig. 1. Prevalence of different type of diarrhea and associated genetic profiles. Group A: Selective nutrients/electrolytes malabsorption due to selective intestinal transport deficiency; **Group B**: Extensive malabsorption due to structural or functional intestinal deficiency**; Group C**: Inflammation ± malabsorption due to deranged intestinal immune-related homeostasis. **ID**: intractable diarrhea; **VEO IBD**: Very early onset inflammatory bowel diseases.

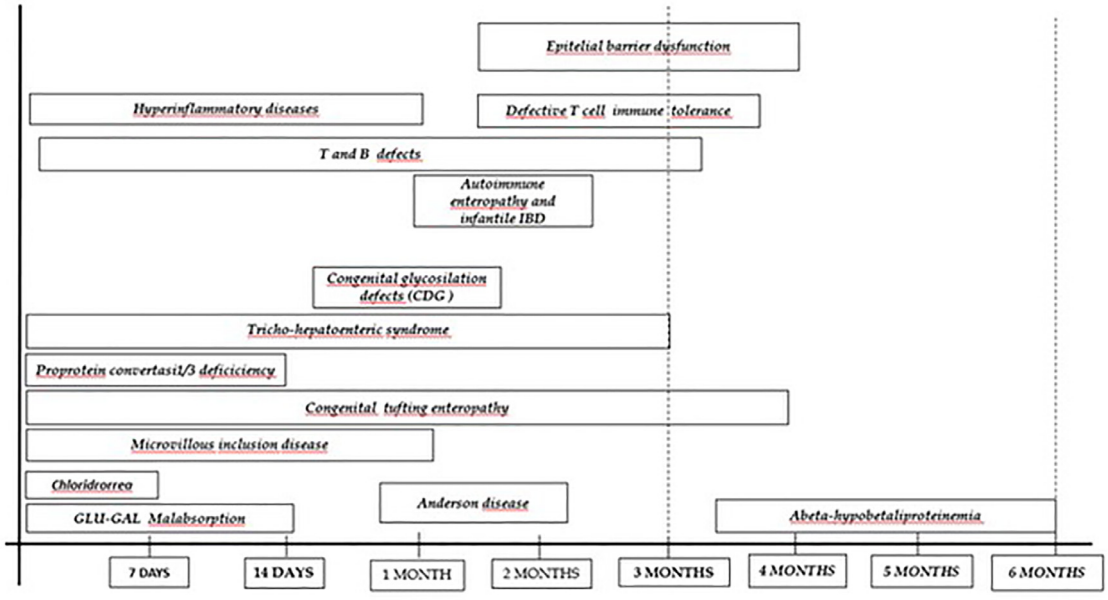

Fig. 2. Age distribution at disease onset according to ID etiology.

diarrhea with selective nutrients/electrolytes epitelial transport defects ($p = 0.0002$). Furthermore, as shown in Fig. 4, secretory diarrhea resulted strongly associated with the need for long-term PN ($p < 0.0001$).

3.3. Main diagnostic strategy

Molecular analysis was the main diagnostic tool in 59 out of the 69 subjects (85.5 %); histology and serologic markers allowed to identify ID etiology in 5 (7.25 %) subjects (one with T a and B lymphocytes defects; 3 with infantile IBD and 1 with autoimmune enteropathy who also showed specific autoimmune serologic pattern). Five patients had unrecognized cause of ID (7.25 %); 3 out of them were affected, nevertheless by genetic diseases, never associated with ID (4.3 %). Overall 62 out of the 69 patients showed genetic diseases (90 %).

4. Discussion

ID are a heterogeneous group of rare diseases and new available treatments, especially if early started based on a prompt diagnosis, can dramatically modify their natural history. In the past most forms of ID were treated only with long-term PN, so HPN became the only way to manage these patients after discharge [12,25,26]. In the last years, knowledge of ID etiology has greatly improved by the advances in molecular analysis [8,27,28]. In the present overview, a genetic disease was found in 84 % of the pa-

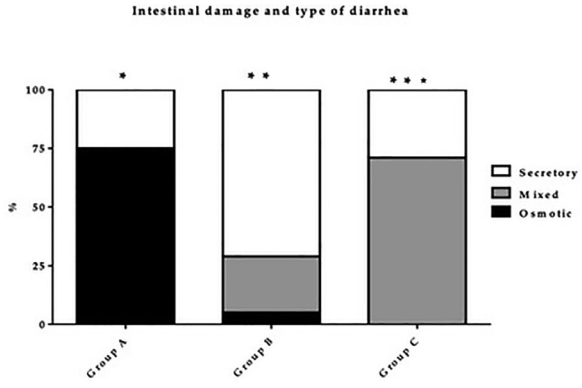

Fig. 3. Group A: Deficiency of nutrients/electrolytes transport; **Group B**: Structural and functional defects of absorption; **Group C**: Defects of intestinal immune-related homeostasis. * $p < 0.0001$ (OR 166; CI 12.95–2102); ** p 0.0010 (OR 6.531; CI 2.196–1943); *** p 0.002 (OR 9.107; CI 2.809–29.53).

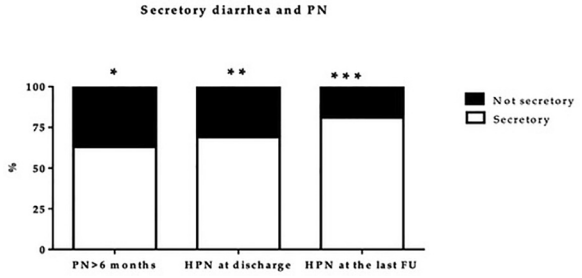

Fig. 4. PN: Parenteral Nutrition; HPN: Home Parenteral Nutrition. FU: Follow up. * p 0.0149 (OR 2.966; CI 1.304–6.745); ** p 0.0007 (OR 4.903; CI 2.008–11.970); *** $p < 0.0001$ (OR 17.16; CI 5.340–55.16).

tients, confirming the growing role of molecular analysis in the diagnosis and management of congenital diarrhea.

In 1990, Ventura et al. [25] reported that 9 out of 18 patients with ID had indefinite etiology of ID (50 %); the remaining 9 patients were affected by autoimmune enteropathy (5 children) microvillous inclusion disease (3 children) and by multiple food allergies (1 child). Subsequently, Catassi et al. [12] described 30 patients with ID, among which 23 with onset within 6 months of life. They found undefined diagnosis in 17 % of the patients but included a quiet different spectrum of etiologies such as digestive congenital malformations (lymphangiectasia and Hirschsprung disease), chronic intestinal pseudo-obstruction, infectious disease and post-enteritis syndrome, that overall could be diagnosed on a clinical basis without requiring complex diagnostic processes as in congenital ID. In 2015, Hayriye and coworkers [4] published a survey from Turkey that included 60 hospitalized patients aged 0 to 24 months at ID onset. he distribution of the etiology ID groups vas very different if compared to the present study: we found higher prevalence of structural and functional defects of absorption (43 % *vs* 14 %); more patterns of defects of intestinal immune-related homeostasis, that in the Turkish study were only allergy and infantile IBD and, finally, lower prevalence of undefined defects (7 % *vs* 32 %).

Interestingly we can argue, based on the present data, that in the last years, the migratory flows could have changed the epidemiology of ID, contributing to the spread of these rare diseases in Western Countries. Although ID are still more common in geographical areas with high rate of consanguinity, as shown by the high rate of consanguinity in the Turkish study (67 %), in Italy in 1999 Catassi et al. [12] found a consanguinity rate of 8 %, that was almost doubled in the present study (15 %).

We classified the single group of ID etiology into three main groups, trying to make a synthesis of the previously suggested classification of both congenital diarrheas and monogenic early onset IBD, that could be overlapped in some cases with ID [8,24,27–30]. So we grouped together the defects in enterocyte structure and in enteroendocrine cell differentiation, because both are responsible for overall malabsorption needing long-term PN, although the clinical phenotype of the diarrhea at fasting was very different (secretory in most defects of enterocyte structure and osmotic in those of enteroendocrine differentiation).

Furthermore, among the defects in intestinal immune-related homeostasis we also included cases of infantile IBD and autoimmune enteropathy without a known genetic etiology, because they could be similar to the VEO-IBD with recognized genetic etiology, with regard to clinical course and management. This group has been expanded by involving many genetic disease not well known in the past. In particular the first sub-group included the dysfunction of the epithelial barrier, including known genetic diseases (mutations in NEMO and COL7A1 genes) and one genetic condition not previously reported as cause of ID (NOX 1 genes mutations).

Inactivating missense variants in NOX1 are indeed recently associated with very early onset IBD (VEO-IBD). This defect leads to partial attenuation in phagocyte oxidase function, that could be associated with inflammatory chronic processes in adults as well as in infants/children [31].

The second group included T and B lymphocytes defects due to mutations in known genes responsible for SCID (RAG1, JAK 3, WAS) and one gene mutation in ICF1 not previously reported. The defects of ICF are responsible for different clinical subtypes of ICF syndromes. Into the spectrum of ICF syndrome, humoral immunodeficiency is more pronounced in ICF1 patients, who can also display some feature of the so-called telomeropathies, such as premature aging of highly regenerative tissues, recurrent infections, aplastic anemia or pulmonary fibrosis. In such diseases HSCT is becoming a more prevalent treatment [32].

Furthermore, we included into the sub-group of hyperinflammatory diseases known gene mutations related to hyperinflammation (HPS1, NLRC4, CDC40, and STXBP2) and one disease with mutated NBAS gene. NBAS-associated disease is a rare autosomal recessive disorder with a broad spectrum of clinical symptoms, mainly involving liver, growth, skeletal system, nervous system, immune system, and musculature. Immunological symptoms and laboratory alterations such as frequent infections, hypogammaglobulinemia, low natural killer (NK) cell numbers, and neutropenia have been observed in more than 60 % of patients with NBAS associated diseases. Dysfunctional NK cell degranulation is responsible for recurrent episodes of hemophagocytic lymphohistiocytosis which is a life-threatening feature of this hyperinflammatory syndrome [33].

The category of the undefined defects included one patient with mutation of mitochondrial DNA (MT-CYB), reported in association with colorectal adenopolyps [4]. Although this specific mitochondrial mutation has never reported as cause of ID, in general mitochondrial mutations could be involved in the etiology of congenital diarrheal diseases [8,34].

In two cases the possible link between gene mutations and development of ID was very difficult to understand: one patient was affected by congenital hypothyroidism due to TSHR mutations and the second by BRAF, a well-known onco-driver gene of the mitogen-activated protein kinase signaling pathway, involved in the development of melanoma and colorectal cancer [35].

Interestingly the present experience identified the window of onset for each etiology. In particular we found that most cases of ID occur in the first two months of life and in particular the first month of life could be considered the window of onset of the deficiency of nutrients/electrolytes transport and of the struc-

tural and functional defects of absorption; only the onset of abetalipoproteinemia occurred later. Most cases of defects of intestinal immune-related homeostasis occur in the second month of life. In several cases, nevertheless, the misrecognition of the ID could be possible, delaying the age at diagnosis, because diarrhea could be confused with urine in the diaper [7,12,14].

Furthermore we found that type of diarrhea was strongly related to the duration of dependence on PN and in particular the prevalence of patients who remained dependent on PN increased over time among patients with secretory ID.

Although the present series allowed to update knowledge about ID, the close relationship between immune disorders and digestive tract could make possible that many cases of ID were referred during the study-period to immunologists and not to gastroenterologists, so leading to the lost of some cases of ID, this fact could be considered the main limitation of our study.

In conclusion, this multicenter study showed that ID is a rare but challenging problem in Italy, although the potential for a diagnosis has greatly improved over time. In particular molecular analysis allowed to identity a genetic defect in 90 % of the patients and to detect new genetic defects responsible for ID, as recently reported by Babcock [22]. Due to the both challenging diagnosis and treatment for many of these diseases, ID infants should be promptly referred to specialized centers for a complete taking care, from molecular analysis to HSCT, when possible. The close relationship between immune system and digestive tract should require a close collaboration between pediatric immunologists and pediatric gastroenterologists, to optimize epidemiologic surveillance and management of ID.

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Conflict of interest

There is no conflict of interest associated with any of the senior author or other co-authors contributed their efforts in this manuscript.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2023.09.002.

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