Full Length Article

COVID-19 in children and young adults with moderate/severe inborn errors of immunity in a high burden area in pre-vaccine era

A. Deyà-Martínez [a,b,c,d,*,1], A. García-García [a,b,c,d], E.A. Gonzalez-Navarro [d,f], L. Yiyi [b,d],
A. Vlagea [d,f], I. Jordan [c,h,i,k], V. Fumadó [c,g,i], C. Fortuny [c,g,i,k,l], M. Español [d,f], C. Launes [c,i,j,k],
A. Esteve-Solé [a,b,d], M. Juan [d,e,f], M. Pascal [d,f,m,2], L. Alsina [a,b,c,d,e,*]

[a] Study Group for Immune Dysfunction Diseases in Children (GEMDIP), Institut de Recerca Sant Joan de Déu, Barcelona, Spain
[b] Clinical Immunology and Primary Immunodeficiencies Unit, Pediatric Allergy and Clinical Immunology Department, Hospital Sant Joan de Déu, Barcelona, Spain
[c] Universitat de Barcelona, Spain
[d] Clinical Immunology Program, Hospital Sant Joan de Déu-Hospital Clínic Barcelona, Barcelona, Spain
[e] Immunotherapy Platform, Hospital Sant Joan de Déu-Hospital Clínic, Universitat de Barcelona, Barcelona, Spain
[f] Department of Immunology-CDB, Hospital Clínic-IDIBAPS, Universitat de Barcelona, Barcelona, Spain
[g] Paediatric Infectious Diseases Unit, Hospital Sant Joan de Déu, Universitat de Barcelona, Barcelona, Spain
[h] Paediatric Intensive Care Unit, Hospital Sant Joan de Déu, Universitat de Barcelona, Barcelona, Spain
[i] Institut de Recerca Sant Joan de Deu, Barcelona, Spain
[j] Paediatrics Department, Hospital Sant Joan de Déu, Barcelona, Spain
[k] CIBER of Epidemiology and Public Health, Madrid, Spain
[l] Translational Research Network in Paediatric Infectious Diseases (RITIP), Madrid, Spain
[m] Spanish Network for Allergy - RETIC de Asma, Reacciones adversas y Alérgicas (ARADYAL), Madrid, Spain

ARTICLE INFO

ABSTRACT

Background: Information regarding inborn error of immunity (IEI) as a risk factor for severe COVID-19 is scarce. We aimed to determine if paediatric patients with moderate/severe IEI got COVID-19 at the same level as the general population, and to describe COVID-19 expression.
Material and methods: We included patients with moderate/severe IEI aged 0–21 years old: cross-sectional study (June2020) to determine the prevalence of COVID-19; prospective study (January2020-January2021) including IEI patients with COVID-19. Assays used: nasopharyngeal swab SARS-CoV-2 PCR and SARS-CoV-2-specific immunoglobulins.
Results: Seven from sixty-five patients tested positive (prevalence: 10.7% (7%–13%)) after the first SARS-COV-2 wave and 13/15 patients diagnosed with COVID-19 had an asymptomatic/mild course.
Conclusions: In our area, prevalence of COVID-19 in moderate/severe IEI paediatric patients after the first wave was slightly higher than in the general population. The majority of patients presented a benign course, suggesting a possible protective factor related with age despite IEI.

1. Introduction

In December 2019, an outbreak caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) started in Wuhan, China, leading to a pandemic of a novel coronavirus disease (COVID-19) [1–3]. After the first COVID-19 case in Spain, reported on 31st January 2020 in La Gomera (Canary Islands), more than 3 million cases [4] of SARS-CoV-2-infected patients had been reported in our country by the end of April 2021, and more specifically >650,000 cases [5] in our region, Catalonia.

In children, a milder course of COVID-19 compared with adults has been reported worldwide [1] with a very low proportion of symptomatic paediatric patients progressing to acute respiratory distress syndrome or multiorgan system dysfunction [6,7].

The main factors related to critical cases are age (>65), male gender, and the presence of certain comorbidities such as diabetes, hypertension, chronic respiratory disease, cancer, and cardiovascular disease [8,9].

Although inborn errors of immunity (IEI) have been assumed to be a risk factor for COVID-19, there is as yet limited information, mainly from adults, and often contradictory at that, about the real impact of COVID-19 on them. Recent studies suggest that only certain IEIs may predispose to severe COVID-19, whereas others could represent a protective factor [10–16]. Nevertheless, reports on paediatric IEI patients are still scarce.

The objectives of the study were first to determine, through a prevalence study, whether children and young adults with moderate/severe IEI living in a high burden area of SARS-CoV-2 infection became infected at the same level as the general population in the first wave, and, second, to describe their clinical presentation of SARS-CoV-2 infection prior to the vaccination era.

2. Material and methods

The study was carried out in a tertiary centre dedicated exclusively to maternal and child healthcare in Barcelona, Catalonia (population > 7.5 millions), Spain, with 314-bed facility, 247.000 outpatient visits per year from all paediatric subspecialties and reference for IEI, attending more than 400 IEI patients. The first wave occurred January-June 2020. Lockdown extended from March 15th to June 21st.

The study design is detailed in Appendices Fig. A.1, with two different periods: 1) a cross-sectional study (prevalence study) in June 2020 (end of first wave) including all moderate/severe IEI patients followed in our Clinical Immunology and Primary Immunodeficiencies Unit who agreed to participate, and 2) a prospective study including all IEI patients in follow-up evaluated for SARS-CoV-2 infection from January 2020 until January 2021 (start of vaccination), collecting clinical and laboratory data of COVID-19 infection. The protocol of this study was reviewed and approved by the ethics committee of our institution. Patients aged 0–21 years old with signed informed consent were included.

COVID-19 cases were defined according to World Health Organization (WHO) criteria [17]. The different IEI categories were based on European Society for Immunodeficiencies (ESID) criteria [18]. The following were considered moderate/severe IEI: severe combined immunodeficiencies, combined immunodeficiencies and other combined immunodeficiencies with syndromic features with moderate/severe lymphopenia (see definition in Appendices Table A.2) [19], severe humoral immunodeficiencies (common variable immunodeficiency (CVID) and agammaglobulinemia), and genetically well-defined and severe cases from other IEI groups.

Patients' clinical and laboratory data were collected from medical charts during the outpatient visit. A specific questionnaire related to COVID-19 in household contacts was used.

The following assays were performed in all patients to confirm SARS-CoV-2 infection: 1) Real-time (RT)-PCR with nasopharyngeal swab. Viral RNA extraction was performed with NucliSENS easyMAG

Table 1
Baseline characteristics of the IEI cohort included in the study.

	$N = 65$[a]
Age	12.98 (2–21.1)
Female	28/65 (47.1%)
Caucasian	50/65 (76.9%)
Group of IEI	
Immunodeficiencies affecting cellular and humoral immunity	7/65 (10.7%)
CID with associated syndromic features	31/65 (47.7%)
Predominantly antibody deficiencies	14/65 (20.6%)
Diseases of immune dysregulation	4/65 (6.1%)
Congenital defects of phagocyte number, function, or both	2/65 (3.1%)
Defects of intrinsic and innate immunity	6/65 (9.2%)
Auto-inflammation disorders	1/65 (1.5%)
Comorbidity	
Respiratory disease	4/65 (6.1%)
Cardiovascular disease	4/65 (6.1%)
Hemato-oncological disease	3/65 (4.6%)
Neurological disease	18/65 (27.7%)
Rheumatological diseases	1/65 (1.5%)
Treatments received from Jan-June 2020	48/65 (73.9%)
Antibiotic treatment	19/65 (29.2%)
Antiviral treatment	3/65 (4.6%)
Antifungal treatment	8/65 (12.3%)
Hydroxychloroquine	1/65 (1.5%)
Regular immunoglobulins	14/65 (21.5%)
Steroids /immunosuppressants[b]	10/65 (15.4%)
COVID-19 epidemiological, clinical and diagnostic information	
Confirmed COVID-19 cases in cohabiting relatives	1/65 (1.5%)
Suspicion of COVID-19 in cohabiting relatives	10/65 (15.1%)
Needs emergency from Jan-June 2020	19/65 (29.2%)
Felt sick from January-June	30/65 (46.1%)
respiratory infection[c]	23/65 (35.4%)
gastrointestinal infection	8/65(12.3%)
cutaneous lesions[d]	8/65 (12.3%
appendicitis	0/65 (0%)
invasive infection[e]	7/65 (10.8%)
Positive SARS-CoV-2 PCR	0/65 (0)
Positive SARS-CoV-2 serology	
IgG + IgA	2/65 (1.5%)
IgA	2/65 (1.5%)
IgM	1/65 (1.5%)
IgG	2/65 (1.5%)

CID: combined immunodeficiency.
[a] Data are expressed as (median (min-max) and percentage).
[b] Immunosupressants used in the PID cohort: mofetil mycophenolate, rapamycin, azathioprine, abatacept.
[c] Respiratory infections: influenza-like syndrome with fever >37 °C, cough without fever, otitis, pneumonia, bronchitis, and others.
[d] Cutaneous lesions: urticaria, pityriasis, papular exanthema.
[e] Invasive infections: sepsis (3), bacterial pneumonia (2), osteoarthicular infection (1), and others (1).

(BioMerieux Laboratories) or MagMAX Viral/Pathogen Nucleic Acid Isolation Kit (Thermo Fisher Scientific) following the manufacturers' instructions. RT-PCR was performed with the COVID-19 Plus RealAmp Kit (Genefinder Laboratories) for detection of the RdRp, E, and N viral genes and the human RNase P gene as internal control; 2) SARS-CoV-2 serology: IgG, IgA, and IgM SARS-CoV-2-specific antibodies were determined by Luminex system against the receptor-binding domain of

the spike glycoprotein, as reported previously. Briefly, 10 μL of plasma was incubated with antigen-coupled beads for 2 h at room temperature with agitation. Plates were then washed 3 times and incubated with a biotinylated secondary antibody (IgM, IgA, or IgG; Sigma-Aldrich) for 45 min at room temperature and with agitation. Plates were washed 3 times and streptavidin-R-phycoerythrin (Sigma-Aldrich) was added for 30 min at room temperature and with agitation. Plates were washed 3 times and beads were resuspended in phosphate-buffered saline (PBS). Plates were read using a Luminex xMAP 100 analyzer; positive values were assigned with MFI ratio 2 SD higher to a serum pool from pre-COVID pandemic samples.

2.1. Statistical analysis

Categorical and continuous variables were described as percentages and median values with ranges (min-max). For the comparative analysis, Chi-square test and Mann-Whitney U test were applied, as appropriate, for the data set. Pearson and Spearman tests were used to identify correlations between quantitative variables. The analysis was carried out using SPSS version 15.0 software (SPSS Inc., Chicago, IL), and statistical significance was set at $P \leq 0.05$.

3. Results

3.1. Cross-sectional study: Prevalence of SARS-CoV-2 infection in IEI patients after the first wave (June 2020)

Of the 76 patients selected with moderate/severe IEI from our cohort, 65 agreed to participate. The baseline characteristics of the cohort are detailed in Table 1 and Table A.1. The median age at the time of the study was 12.9 years old (2–21.1), 47.1% (28/65) were female, and the predominant IEI group was combined immunodeficiency with associated syndromic features (47.7%), followed by predominantly antibody deficiencies (20.6%). Seventy-three percent of the patients received some treatment from January to June 2020: 15.4% immunosuppressants (mofetil mycophenolate, rapamycin, azathioprine, abatacept, or steroids) and 21.5% regular immunoglobulin replacement treatment (IgRT).

Sixteen percent of the patients were exposed to confirmed/suspected COVID-19 cohabiting relatives (not all tested for SARS-CoV-2, due to the limited testing during the first wave of the pandemic in Spain). A total of 7 IEI patients were confirmed as having been infected with SARS-COV-2 by means of SARS-CoV-2 serologies (7/7) (Table 1), which represents a prevalence of 10.7% (7%–13%).

3.2. Prospective study: Clinical expression of COVID-19 in IEI patients

Prior to the vaccination era (that is, January 2020 – January 2021), a total of 15 IEI patients were confirmed as infected by SARS-CoV-2: 2/15 by positive PCR and 13/15 by positive serologies with/without positive PCR. Of these positive patients, 60% (9/15) presented some degree of clinical expression, 7/9 mainly mild symptoms including headache, low fever, flu-like syndrome, cough, upper airway congestion, odynophagia or taste and smell disturbances; and 2/9 required admission to hospital with interstitial pneumonia. The two admitted patients were siblings with MyD88 deficiency. The main characteristics of these 2 patients and of the COVID-19 episode are depicted in Appendices Fig. A.2.

4. Discussion

The present study was designed to analyse the prevalence of SARS-CoV-2 infection in a cohort of children and young adults with moderate/severe IEI; and it describes the main clinical characteristics of COVID-19 in this paediatric cohort prior to the vaccination era. Our results reveal an infection rate among these patients slightly higher than in the general population in the same region during the study period

(data from national seroprevalence survey of the general population in Catalonia in June 2020, 5.9% 5.-7.1) [5]. During one year's follow-up (Jan 2020-Jan 2021), the majority of infected patients showed mild/absence of COVID-19-related symptoms and only two (2/15; 13.3%) needed admission to hospital with respiratory disease. As far as we know, this is the first study focused on SARS-CoV-2 infection in paediatric patients with IEI.

Most IEI patients have direct or indirect impairment of some of the components of the anti-viral response, in most cases presenting viral infection susceptibility [8]; moreover, immunocompromising conditions have been associated with more severe outcomes with non-COVID-19 coronavirus infections in children [20]. Thus, IEI was initially listed as one theoretical risk factor for symptomatic/severe COVID-19. Our cohort (Table 1) included patients from 7/10 different IEI categories, the most frequent being combined immunodeficiency with syndromic features and humoral immune deficiencies, which are also the most frequent groups in current classifications. Thus, our cohort is representative of other large published cohorts [21].

Data obtained in our study show a slightly higher prevalence (10.7%; 7%–13%) when compared to the general population in Catalonia in the same period with 5.9% (5.0%–7.1%), although IEI patients followed the same infection prevention recommendations as the general population, and even more strictly and sooner than officially recommended in some cases. To date, no data regarding the prevalence of COVID-19 among patients with IEI have been published against which we could compare our data.

Despite this higher prevalence, IEI patients from our cohort did not develop severe COVID-19 symptoms. Data from healthy children in Spain aged <2 years old, 2-4, 5–14, and 15–29 show that only 2.3%, 0.6%, 0.4%, and 1.2%, respectively were admitted to hospital, and only 10 deaths have been reported up to the end of April 2021 in patients <14 years old [22]. Despite the lack of information related specifically to adolescents, recent reports suggest that COVID-19 often presents a more severe course in adolescents than in younger children [23]. In our cohort, 2/15 (13.3%) were admitted to hospital, both adolescents (17 and 19 years old). Nevertheless, they did not suffer severe complications nor mortality, suggesting that their clinical evolution was closer to other healthy children and young adults than to older adults, in whom higher hospitalization and mortality rates (hospitalization/mortality rate in group age 60–69 is 13.9%/1.5%; 70–79% is 23.6 /5.2% and > 80 34%/16%) have been reported [23].

The available data regarding COVID-19 in IEI patients, mainly adults, are inconsistent. The European cohort, led by the ESID and published by *Meyts and cols et al*, as well as the experience of Israel, show good clinical courses [10,24]; the Italian experience with humoral deficiencies even suggests a possible protective factor for severe COVID-19 associated with X-linked- agammaglobulinemia or dominant negative STAT3 defects, probably because of its interference with IL-6 production [11–13]. In contrast, other experiences with larger cohorts suggest higher mortality rates and severity among patients with IEI[14,25].

In the majority of these cohorts, paediatric patients are underrepresented. Of note, *Delavari* et al. reported on a cohort of 19 patients with IEI and COVID-19. The majority of them (84%) were < 20 years of age and 8/19 died, of whom 5 were younger than 20. Those data contrast with previous studies and the low mortality rate among young cases in the general population. The difference may arise from the fact that 10 of the 19 cases included were severe combined immunodeficiency or familial lymphohistiocytosis without HSCT [26]. Thus, it seems clear that IEIs are a wide and heterogeneous group of disorders for which SARS-CoV-2 susceptibility differs widely.

From the limited information available regarding IEI and COVID-19, it seems that certain immunodeficiencies carry a higher risk than others; specifically, CVID with dysregulation [14,25] and defects involving type I interferon pathways [15] have been associated with higher hospital admission, severity, and mortality. The reasons why CVID is related with higher mortality and severity remain unclear; the presence of underlying

Table 2
Baseline and clinical characteristics of SARS-CoV-2 infected IEI patients.

	Age (years)	Gender	IEI	Chronic treatments	Positive household contacts	COVID-19 WHO classification*	Symptoms	Positive serologies	PCR	Specific COVID-19 treatment
Cross-sectional (January-June 2020)										
P1	13	female	Jacobsen syndrome + CVID pattern	no	suspected	1	Cough	IgG and IgA	−	no
P2	15	female	Down syndrome	no	suspected	1	Asymptomatic	IgG	−	no
P3	11	female	PGM3 deficiency	Dupilumab	suspected	1	Fever and interstitial pneumonia	IgA	−	no
P4	17	male	Di George with mod/ severe lymphopenia	no	no	1	Asymptomatic	IgG	−	no
P5	15	male	STAT1GOF	Hydroxy-chloroquine Fluconazole	no	1	Cough and upper airway congestion	IgA	−	no
P6	10	male	Jacobsen syndrome + mod/severe lymphopenia	no	no	1	Cough and upper airway congestion	IgG and IgA	−	no
P7	5	male	Di George with mod/ severe lymphopenia	no	no	1	Cough	IgM	−	no
Patients collected from June 2020–January 2021										
P8	14	female	CVID	no	no	1	Asymptomatic	Negative	+	no
P9	22	male	Chronic granulomatous disease	Itraconazole SMZ-TMP	no	1	Asymptomatic	IgG and IgM	np	no
P10	8	male	XLA	IgRT	confirmed	1	Asymptomatic	IgM	+	no
P11	19	male	Ataxia telangiectasia	IgRT SMZ-TMP Azithromycin	suspected	1	Fever, headache, and asthenia	negative	+	no
P12	17	female	CVID	no	suspected	1	Asymptomatic	IgG and IgM	+	no
P13	16	female	MyD88 deficiency	no	suspected	2	Fever, headache, asthenia, and interstitial pneumonia	IgG and IgM	+	Steroids Heparin Antibiotics
P14	19	male	MyD88 deficiency	no	suspected	2	Fever, headache, asthenia, and hypoxic interstitial pneumonia	IgG and IgM	+	Steroids Heparin Remdesivir Antibiotics
P15	17	male	ALPS syndrome	no	no	1	Headache, upper airway congestion, odynophagia, taste and smell disturbances	IgM	+	no

mod/severe: moderate/severe; SMZ-TMP: sulfamethoxazole-trimethoprim; nv: non valuable; np: not performed.
SMZ-TMP: sulfamethoxazole-trimethoprim.

morbidity such as chronic lung disease or the need for immunoglobulins, leading to more severe immunodeficiency status, have been proposed as important factors[10,25.] In our cohort, the majority of patients presented a mild clinical course, even those suffering an IEI theoretically related to worse COVID-19 outcome, such as CVID. Surprisingly, the two patients with more pronounced clinical expression were siblings affected with MyD88 deficiency, which had been reported not to be associated with susceptibility to viral infections [27]. To date only 3 cases of MyD88 deficiency and COVID-19 have been reported [28]. These 3 cases were adolescent siblings, and they displayed differing clinical evolutions: two females required ICU and mechanical ventilation, while the male presented a milder course. This highlights the fact that even with the same immune condition, the ultimate clinical course of COVID-19 might differ, because other factors may contribute to the clinical development. In the siblings with MyD88 deficiency, older age and/or obesity present in patient B probably played a role in the severity of his case. Interestingly, although some of the patients infected in our cohort have an immune disorder with dysregulation, none of them developed MIS-C, a specific and serious paediatric COVID-19 post-infectious complication [29].

The reason why young patients with IEI are clinically more similar to healthy children than to adult IEI patients with COVID-19 remains unclear. One reasonable explanation is the absence of comorbidity in paediatric patients, as opposed to adults, especially in CVID patients. Also, children seem to be intrinsically resistant to SARS-CoV-2,

attributable to a higher ACE II concentration which seems to offer a protective effect on severe clinical SARS-CoV-2 infection, along with higher 'trained' innate immune system due to vaccines and other respiratory viral infections during infancy [30], which is especially relevant in paediatric IEI patients who have recurrent upper respiratory tract infections.

Finally, regarding the diagnostic test performed in our patients, all of our patients except two were diagnosed by serology test. Curiously, 2 patients were diagnosed only by SARS-CoV-2 specific IgA. Different studies have been published until now regarding the specific SARS-CoV-2 serology assays and their value as a diagnostic test for the infection, and concretely some of them focus in specific IgA antibodies: they have shown that IgA specific antibodies could grow early and strongly than IgM and IgG antibodies [31,32]. Since the two patients from our cohort (patients 3 and 5; Table 2) that were considered infected only by positive IgA belong to the seroprevalence study (cross-sectional), it may be well that we detected COVID-19 infection during early stages, before IgG/M seroconversion. On the other hand, although none of them have humoral immunodeficiency they are immunodeficient patients, and this may have an impact on their antibody production.

In conclusion, in our cohort including moderate/severe children and young adults with IEI, the infection rate was slightly higher than that observed in the general population, despite patients' following the same infection prevention recommendations. Even with this higher rate, no severe COVID-19 was observed; only 2 patients with MyD88 deficiency

required hospital admission and both showed good clinical evolution. Among possible explanations, the absence of comorbidities linked to COVID-19 severity, the possibility that only certain IEI are really risk factors for developing severe COVID-19, and a possible protection caused by age < 21 should be mentioned. Studies with larger samples are needed to confirm the trend observed in this study. In the event that this observation is borne out, this could influence future prevention measures in this special population.

5. Conclusions

This is the first study focused on paediatric patients with IEI and the impact on COVID-19. Our data show a higher infection rate, but without clinical severity except in two patients with MyD88 deficiency, suggesting that other factors such as younger age, absence of comorbidity, and more highly 'trained' immunity due to greater exposure to viral respiratory infections in IEI patients might be more important determinants of COVID-19 outcome than the immune deficiency *per se*. In the event that these data are confirmed in larger paediatric IEI cohorts, these findings could have an impact on future SARS-CoV-2 infection prevention recommendations for this population.

Declarations of interest
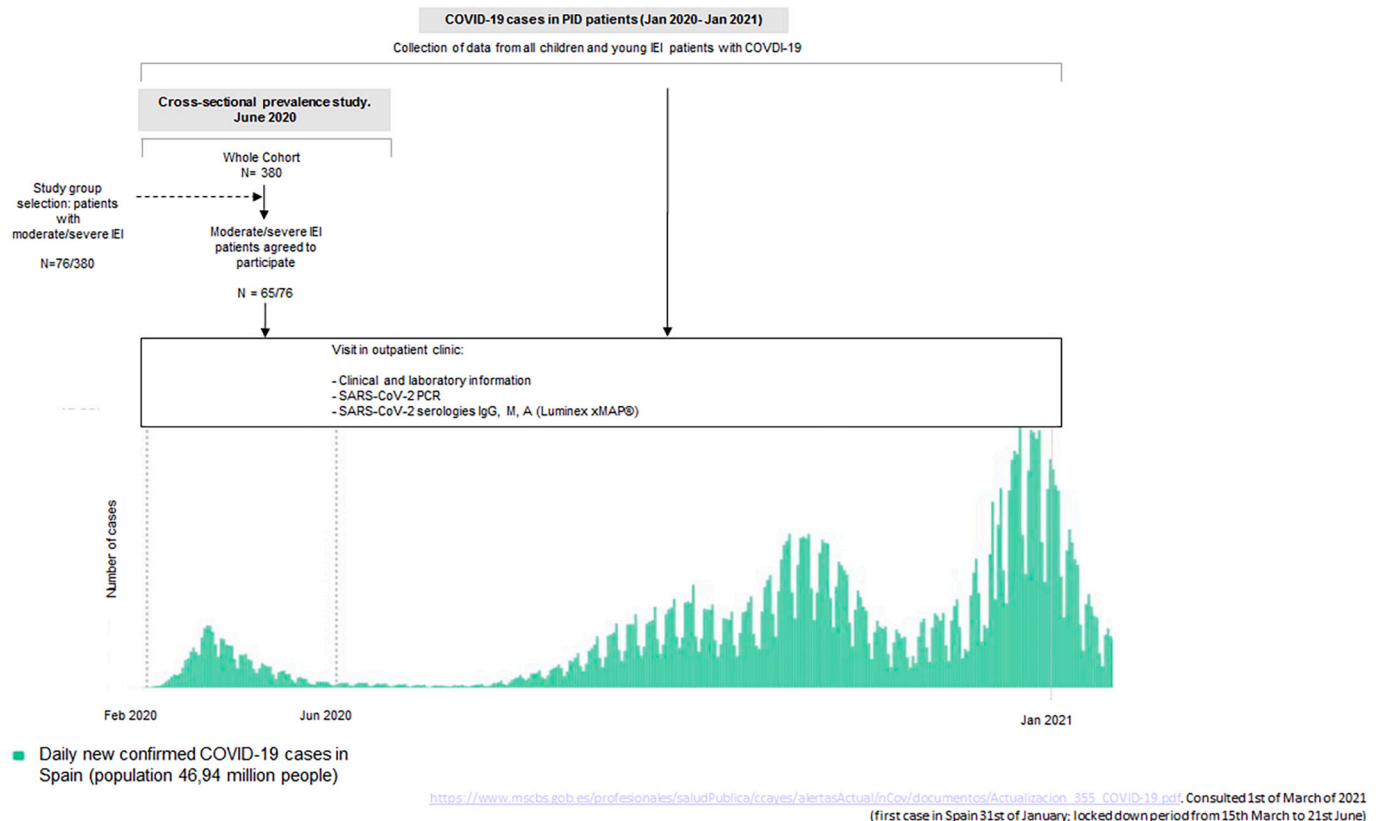
None.

Appendix A. Appendices

Fig. A.1. Study design.

https://www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov/documentos/Actualizacion_355_COVID-19.pdf. Consulted 1st of March of 2021 (first case in Spain 31st of January; locked down period from 15th March to 21st June).
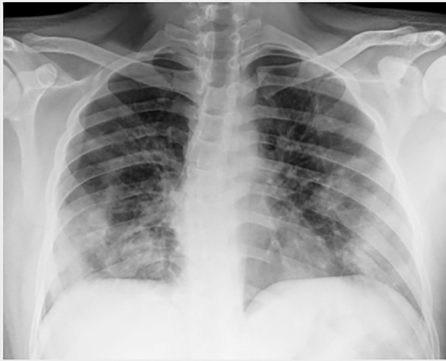
Patient	A	B
Age	17	19
Gender	Female	Male
Immunodeficiency	MyD88 deficiency	MyD88 deficiency
Baseline treatments	none (cotrimoxazole prophylaxis stopped 2 years before)	none
Previous comorbidity	Pneumopathy post-necrotizing pneumonia	Obesity (BMI 31.2)
Disease characteristics		
Admission days	6 days	5 days
Clinical presentation	Fever, odynophagia, cough, interstitial pneumoniae	Odynophagia, cough, hypoxic interstitial pneumoniae
Blood parameters		
Ferritin (max.)	310 ug/L*	305 ug/L**
Platelets (min.)	147000/mm3*	157000/mm3**
Anaemia(min.)	12.6 g/dl*	13.5 g/dl**
Lymphocytes (min.)	600/mm3*	900 /mm3**
D-dimer	1.94 mg/L*	0.33 mg/L**
CRP	108 mg/L*	69.1 mg/L**
Specific COVID-19 treatments	ceftriaxone, dexamethasone, heparin	Oxygen (nasal canules), Remdesivir, ceftriaxone, methylprednisolone, heparin
X- ray		

Fig. A.2. Clinical description of two patients with moderate COVID-19.

In this figure the two patients with the more severe COVID-19 from our cohort are described. Both patients are siblings, with Myd88 deficiency, presenting both respiratory symptoms with an interstitial pneumonia. Curiously, the patient A, presented the worst analysis parameters while the patient B presented the worst clinical evolution needing oxygen.

BMI: Body mass index; *the lowest and highest values were observed at 3rd day of admission **only one blood analysis. min: minumum; max.: maximum.

Table A.1
Specific IEI included in the study ($n = 65$).

IEI group	Number of patients and specific disease
Immunodeficiencies affecting cellular and humoral immunity	**7/65 (10.7%)**
Combined immunodeficiencies with associated syndromic features	2 RFXANK SCID 1 Hyper IgM CD40L 1 CID 3 idiopathic CD4+ lymphopenia **31/65 (47.7%)**
	1Kabuki syndrome 5 Ataxia-telangiectasia 10 CATCH22 2 Jacobsen syndrome 3 Down syndrome 1 Trico-hepato-enteric syndrome 1 CHARGE syndrome 2 Mitochondrial disease 6 other syndromes
Predominantly antibody deficiencies	**14/65 (20.6%)**

Table A.1 (*continued*)

IEI group	Number of patients and specific disease
Diseases of immune dysregulation	3 Bruton's agammaglobulinemia 11 CVID **4/65 (6.1%)** 1 XIAP-like (no genetics) 1 CTLA4 1 STAT3 GOF 1 undefined severe disorder of immune dysregulation (no genetics)
Congenital defects of phagocyte number, function, or both	**2/65 (3.1%)** 2 CGD
Defects in innate immunity	**6/65 (9.2%)** 1 WHIM syndrome (CXCR4 GOF) 3 CMC (STAT1 GOF) 1 TLR3 deficiency 1Hyper IgE syndrome (PGM3)
Overlap autoinflammatory-immunodeficiency disease	**1/65 (1.5%)** 1 APLAID syndrome (PLCG2 deficiency)

SCID: severe combined immunodeficiency; CID: combined immunodeficiency; CVID: common variable immunodeficiency; CGD: chronic granulomatous disease; WHIM (warts, hypogammaglobulinemia, immunodeficiency, myelokatexis); CMC: chronic mucocutaneous candidiasis.

Table A.2
Definition of moderate/severe lymphopenia [18].

	CD4+absolute count/%		
	birth-11 months	1–5 years	> 5 years
Moderate immunosuppression	750–1499/15%–24%	500–999/ 15–24%	200–499/15%–24%
Severe immunosuppression	<750/<15%	<500/<15%	<200/<15%

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