Immune Netw. 2022 Aug;22(4):e30
https://doi.org/10.4110/in.2022.22.e30
pISSN 1598-2629·eISSN 2092-6685

IMMUNE NETWORK

Correspondence

Outstanding Features of COVID-19 Overlapping Primary Immunodeficiency in Children

Qi Jiang, Qian Yang, Man Man Niu, Peng Hu *

Department of Pediatrics, The First Affiliated Hospital of Anhui Medical University, Hefei 230022, China

Received: May 13, 2022
Revised: Jun 13, 2022
Accepted: Jul 11, 2022
Published online: Aug 4, 2022

***Correspondence to**
Peng Hu
Department of Pediatrics, The First Affiliated Hospital of Anhui Medical University, No. 218 Ji-Xi Road, Hefei 230022, China.
Email: hupeng28@aliyun.com

ORCID iDs
Qi Jiang
https://orcid.org/0000-0003-0959-5955
Qian Yang
https://orcid.org/0000-0003-4267-1059
Man Man Niu
https://orcid.org/0000-0001-8038-1867
Peng Hu
https://orcid.org/0000-0002-2144-9806

Conflict of Interest
The authors declare no potential conflicts of interest.

Abbreviations
COVID-19, coronavirus disease 2019; CRP, C-reactive protein; IQR, interquartile range; PID, primary immunodeficiency; XLA, X-linked agammaglobulinemia.

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2, is a highly transmittable and contagious infection among the general population, especially in individuals with immune defects regardless of primary immunodeficiencies (PID) or secondary immunodeficiencies caused by infectious agents and drugs. PID, caused by genetic defects, is referred to the inability to produce a normal complement of Abs or immunologically sensitized T cells especially in response to specific Ags. Registry and survey data from a variety of sources reveal an incidence for all PID ranging from 1 in 10,000 to 1 in 2,000 live births. Individual PID may be rare, but altogether, they are exactly frequent. Admittedly, little is known, to date, about the clinical features of COVID-19 overlapping PID.

A total of 7 eligible studies (1-7) encompassing 166 children with COVID-19 overlapping PID were incorporated in this correspondence, through searches of PubMed, Web of Science and Medline from inception to January 2022 (**Table 1**), after exclusion of studies with fewer than 10 PID children.

Males outnumbered females (101:65), with a median age of 9.1 years (interquartile range: 5.3–14.8). Fever (59.0%) was the most commonly reported symptom of COVID-19 occurring in PID patients, followed by upper respiratory symptoms (40.4%), gastrointestinal involvements (19.3%) and rash (5.4%). The disease severity of COVID-19 was defined following the NIH criteria: 14.2% of patients were critical, 9.8% severe, 9.0% moderate, 46.6% mild and 20.4% asymptomatic, respectively. After treatment, 86.7% of patients recovered, and 13.3% died. Despite the limited information on immune/inflammatory profiles, Castano-Jaramillo et al. (4) documented that lymphopenia and elevated inflammatory markers were outstanding in these patients with COVID-19 overlapping PID.

In this correspondence, we summarized 4 outstanding features of COVID-19 overlapping PID in children. First, male predominance was observed in COVID-19 patients with PID, mainly due to the unbalanced gender distribution in PID. According to the data from one of the biggest referral centers for PIDs in China (8), X-linked agammaglobulinemia (XLA) was reported as the most frequent phenotype, accounting for 22.1% of PID patients; moreover, after a 6-year follow-up, all patients with XLA survived after immunoglobulin replacement therapy. Therefore, the high proportion and long-term survival of patients with X-linked immunodeficiencies are proposed to be the substantial causes of male predominance in

Table 1. The summary of available studies on coronavirus disease 2019 in primary immunodeficiency children

Variables	Karakoc Aydiner' report (1)	Goudouris' report (2)	Esenboga' report (3)	Castano-Jaramillo' report (4)	Deyà-Martínez' report (5)	Meyts' report (6)	Delavari' report (7)	Total
No. of cases	22	57	11	16	12	32	16	166
Male/female ratio	13:9	31:26	6:5	13:3	1:1	11:5	5:3	101:65
Median age (yr) (IQR)	7.4 (4.5–12.6)	10.4 (4.3–13.5)	9.0 (3.8–13.0)	11.5 (4.3–15.0)	13.5 (10.3–16.0)	7.5 (7.5–13.5)	8.0 (0.8–11.7)	9.1 (5.3–14.8)
Manifestations, No. (%)								
Fever	15 (68.2%)	29 (50.9%)	6 (54.5%)	13 (81.3%)	2 (16.7%)	20 (62.5%)	13 (81.3%)	98 (59.0%)
Fash		6 (10.5%)		1 (6.3%)		2 (6.3%)		9 (5.4%)
Hypotension or shock				4 (25%)		4 (12.5%)	1 (6.2%)	9 (5.4%)
Gastrointestinal symptoms	6 (27.3%)	10 (17.5%)	1 (9.1%)	4 (25%)		6 (18.6%)	5 (31.3%)	32 (19.3%)
Upper respiratory symptoms	11 (50.0%)	15 (26.3%)	6 (54.5%)	6 (37.5%)	5 (41.7%)	16 (50.0%)	8 (50.0%)	67 (40.4%)
Asymptomatic	3 (13.6%)	18 (31.6%)			4 (33.3%)	8 (25.0%)		33 (20.4%)
Laboratory findings, No. (%)								
Lymphopenia	6 (27.3%)			11 (68.6%)			7 (43.8%)	24 (14.5%)
Elevated CRP	11 (68.2%)			8 (50.0%)			12 (75.0%)	31 (18.7%)
Elevated D-dimer	12 (54.5%)			8 (50.0%)				20 (12.0%)
Elevated serum ferritin	4 (18.2%)			6 (37.5%)				10 (6.0%)
Disease severity (%)		Mild 50.8% Moderate 5.3% Severe 5.3% Critical 7.0%	Mild 90.9% Moderate 9.1%	Mild 50.0% Moderate 6.3% Severe 18.77% Critical 25.0%	Mild 16.7% Moderate 50.0%	Mild 43.8% Moderate 12.5% Severe 18.7%	Mild 43.7% Severe 6.3% Critical 50.0%	Mild 46.6% Moderate 9.0% Severe 9.8% Critical 14.2%
Outcome (%)	Recovered 77.3% Death 22.7%	Recovered 94.7% Death 5.3%	Recovered 100%	Recovered 75.0% Death 25.0%	Recovered 100%	Recovered 93.8% Death 6.3%	Recovered 50% Death 50%	Recovered 86.7% Death 13.3%

IQR, interquartile range; CRP, C-reactive protein.

Author Contributions

Conceptualization: Hu P; Data curation: Jiang Q, Yang Q; Writing - original draft: Jiang Q, Yang Q, Niu MM; Writing - review & editing: Niu MM, Hu P.

PID. Second, asymptomatic status occurred in 20.4% of patients with COVID-19 overlapping PID, subjected to a 4.6-fold increase than that in previously healthy individuals (4.4%) from a Chinese epidemiological study (9). Although immunodeficient patients appear more vulnerable to various infectious agents, the long-term routine immunoglobulin replacement therapy against PID may be coincident with the management of COVID-19 and alleviate disease severity, to some extent. Third, lymphopenia is commonly recognized as both an early feature of PID and a critical signal of complicated infections including COVID-19. A retrospective study from China (10) indicated that lymphocyte percentage exhibited a persistent decline in 80% of COVID-19 decedents and reached the lowest level within 2 wk after disease onset. However, it is obscure whether this feature is also presented, or even more obvious in COVID-19 patients with underlying PID. Last but the most important, the case-fatality ratio in the present PID children was 13.3%, significantly higher than that in the previously healthy group. Therefore, COVID-19 overlapping PID dramatically increases the overall risk of death.

In summary, we preliminarily analyzed the clinical characteristics of 166 children with COVID-19 overlapping PID, and identified male predominance, asymptomatic status, lymphopenia and higher mortality as the outstanding features relative to previously healthy individuals. As for further prevention and management of COVID-19 in PID individuals, at least 3 aspects should be brought to the attention of clinicians, including additional medical care, earlier initiation of immunotherapy and long-term outcomes.

REFERENCES

1. Karakoc Aydiner E, Bilgic Eltan S, Babayeva R, Aydiner O, Kepenekli E, Kolukisa B, Sefer AP, Yalcin Gungoren E, Karabiber E, Yucel EO, et al. Adverse COVID-19 outcomes in immune deficiencies: inequality exists between subclasses. *Allergy* 2022;77:282-295.
PUBMED | CROSSREF
2. Goudouris ES, Pinto-Mariz F, Mendonça LO, Aranda CS, Guimarães RR, Kokron C, Barros MT, Anísio F, Alonso ML, Marcelino F, et al. Outcome of SARS-CoV-2 infection in 121 patients with inborn errors of immunity: a cross-sectional study. *J Clin Immunol* 2021;41:1479-1489.
PUBMED | CROSSREF
3. Esenboga S, Ocak M, Akarsu A, Bildik HN, Cagdas D, Iskit AT, Tezcan I. COVID-19 in patients with primary immunodeficiency. *J Clin Immunol* 2021;41:1515-1522.
PUBMED | CROSSREF
4. Castano-Jaramillo LM, Yamazaki-Nakashimada MA, O'Farrill-Romanillos PM, Muzquiz Zermeño D, Scheffler Mendoza SC, Venegas Montoya E, García Campos JA, Sánchez-Sánchez LM, Gámez González LB, Ramírez López JM, et al. COVID-19 in the context of inborn errors of immunity: a case series of 31 patients from Mexico. *J Clin Immunol* 2021;41:1463-1478.
PUBMED | CROSSREF
5. Deyà-Martínez A, García-García A, Gonzalez-Navarro EA, Yiyi L, Vlagea A, Jordan I, Fumadó V, Fortuny C, Español M, Launes C, et al. COVID-19 in children and young adults with moderate/severe inborn errors of immunity in a high burden area in pre-vaccine era. *Clin Immunol* 2021;230:108821.
PUBMED | CROSSREF
6. Meyts I, Bucciol G, Quinti I, Neven B, Fischer A, Seoane E, Lopez-Granados E, Gianelli C, Robles-Marhuenda A, Jeandel PY, et al. Coronavirus disease 2019 in patients with inborn errors of immunity: an international study. *J Allergy Clin Immunol* 2021;147:520-531.
PUBMED | CROSSREF
7. Delavari S, Abolhassani H, Abolnezhadian F, Babaha F, Iranparast S, Ahanchian H, Moazzen N, Nabavi M, Arshi S, Fallahpour M, et al. Impact of SARS-CoV-2 pandemic on patients with primary immunodeficiency. *J Clin Immunol* 2021;41:345-355.
PUBMED | CROSSREF
8. Wang LL, Jin YY, Hao YQ, Wang JJ, Yao CM, Wang X, Cao RM, Zhang H, Chen Y, Chen TX. Distribution and clinical features of primary immunodeficiency diseases in Chinese children (2004–2009). *J Clin Immunol* 2011;31:297-308.
PUBMED | CROSSREF
9. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, Tong S. Epidemiology of COVID-19 among children in China. *Pediatrics* 2020;145:e20200702.
PUBMED | CROSSREF
10. Tan L, Wang Q, Zhang D, Ding J, Huang Q, Tang YQ, Wang Q, Miao H. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. *Signal Transduct Target Ther* 2020;5:33.
PUBMED | CROSSREF