Original Article

Case series of COVID-19 outcomes in adult patients with inborn errors of immunity

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ABSTRACT

Background: Since the onset of the COVID-19 pandemic, a main challenge for clinicians and public health decision-makers has revolved around risk stratification in vulnerable populations, in particular individuals with inborn errors of immunity (IEI). However, available reports of the clinical course of COVID-19 in patients with IEI show wide variability, from a complete lack of symptoms to severe and complicated disease.

Objective: To present the clinical features and outcomes of SARS-CoV-2 infection in adult patients with IEI.

Methods: We performed a retrospective chart review documenting patient characteristics and clinical course of SARS-CoV-2 infection between December 2021 and July 2022.

Results: Ten adult patients with IEI followed in our center were diagnosed with COVID-19, as determined by RT-PCR or rapid antigen testing. IEI in this cohort included those with humoral and combined immunodeficiencies, as well as phagocytic defects. An underlying lung comorbidity was identified in 3 patients. Symptoms were mostly mild and self-limiting, and no severe outcomes, complications, or mortality were noted in this study.

Conclusions: We suggest that patients affected by a wide range of both humoral and combined IEI may demonstrate resilience, while highlighting the possible protective effects of vaccination and immunoglobulin replacement in this population.

Statement of Novelty: We report on the mild COVID-19 clinical course of 10 adults with IEI.

Introduction

In March 2020, Coronavirus disease 2019 (COVID-19) caused by the novel coronavirus SARS-CoV-2 was declared a global pandemic (Cucinotta and Vanelli 2020; Kahn and Mcintosh 2005). Among previously healthy individuals, the clinical spectrum of COVID-19 is broad, ranging from asymptomatic infection to severe respiratory complications, myocarditis, and multi-system failure. Given the high burden of disease seen in many immunocompetent hosts, concern has risen in regards to the possible impact of COVID-19 on immunocompromised patients. Indeed, reports published during the early stages of the pandemic showed evidence of hyperinflammation, acute respiratory distress syndrome, cytopenias, and increased mortality among patients with inborn errors of immunity (IEI) (van Damme et al. 2020; Jin et al. 2020; Castano-Jaramillo et al. 2021; Shields et al. 2021; Meyts et al. 2021). Additionally, a prolonged recovery period of up to 60 days was reported in patients with

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X-linked agammaglobulinemia (Giardino et al. 2022; Esenboga et al. 2021).

Since the publication of the above reports, additional variables have entered the clinical equation of COVID-19 in IEI patients. These have included the availability of vaccines against SARS-CoV-2, specific therapies such as monoclonal neutralizing antibodies, and the rise of new variants and subvariants. Thus, it is pertinent to continuously re-evaluate the severity of COVID-19 in IEI patients and determine the need for targeted interventions in this population. We hereby review our center's recent experience in following 10 adult patients with a wide variety of IEI affected by COVID-19. All patients had been fully vaccinated against SARS-CoV-2, and most had also been receiving immunoglobulin replacement. Our patients, including those with underlying lung disease, overall showed mild disease symptoms with no complications or need for hospital admission.

Methods

In this retrospective study, we reviewed the charts of patients with IEI followed in our center who were diagnosed with COVID-19 infection between December 2021–July 2022. Patients were included if they consented to participate in the Canadian Centre for Primary Immunodeficiency Registry and Tissue Bank, approved by the Hospital for Sick Children Research Ethics Board (REB protocol # 1000005598). Information regarding patient demographics, underlying immune diagnoses, presence of an underlying lung disease, clinical course of COVID-19 infection, laboratory evaluation and therapeutic measures used, was collected.

Results

Patient characteristics

Between December 2021 and July 2022, 10 adult patients (7 females and 3 males, aged 23–69 years, median age: 38 years) followed by our center for IEI were diagnosed with COVID-19, as determined by RT-PCR or rapid antigen testing (Table 1). With regards to underlying immune diagnosis, 5 patients had a humoral immunodeficiency (CVID, Roifman syndrome), 2 patients had a combined immunodeficiency, 2 patients had immune dysregulation features (currently undergoing genetic work up), and 1 patient had chronic granulomatous disease (CGD). Three patients had an underlying lung condition, including asthma and (or) interstitial lung disease.

Clinical course, immunoglobulin replacement, and vaccination

The most frequent presenting symptoms were upper respiratory tract symptoms such as cough and coryza, while fever was present only in 3 patients. Respiratory complications or asthma exacerbations were not observed in any of the patients. Duration of symptoms ranged from 3 days to 3 weeks (median: 10 days). All patients were treated as outpatients. All patients had been vaccinated with 2–4 doses of specific vaccines against SARS-CoV-2. Eight patients had been receiving regular immunoglobulin replacement therapy at the time of acquiring SARS-CoV-2 infection. P10, a 35-year-old woman with CGD, contracted COVID-19 twice; the first infection occurred 5 months post-vaccination and included 3 days of fever, cough and upper respiratory illness (URI), while the second episode included mild URI symptoms.

COVID-19 treatments

Specific treatments were given to 4 out of 10 patients. P1, a 64 year-old female with recurrent opportunistic lung infections and an unknown genetic diagnosis, was treated with an anti-SARS-CoV-2 monoclonal antibody (sotrovimab) on day 7 of her symptoms and reported improvement 24 hours post-treatment. Sotrovimab was also given to P5, a 39-year-old female with DOCK8 deficiency, and P7, a 41-year-old female with immune dysregulation disorder, autoimmune hemolytic anemia, dysgammaglobulinemia and status post-splenectomy, who both had a mild course. P6, a 23-year-old female with Roifman Syndrome received paxlovid and remained well. Non-specific therapies included empiric antimicrobials and prednisone for P2 due to a prolonged course of disease, prescribed by his family physician for presumed bronchitis.

Follow up

At the time of study conclusion, median follow-up period from the time of infection has been 4 months (range: 0.5–7 months). At present, all patients remain complication-free following infection, with full symptom resolution and no long-term sequelae.

Table 1: **Patients characteristics and clinical features.**

Patient number	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10
Gender	F	M	M	F	F	F	F	F	M	F
Age (years)	64	69	45	28	39	23	41	37	27	35
IEI diagnosis	CID	CVID	Roifman syndrome	Humoral immunodeficiency	Hyper Ige syndrome, DOCK8 deficiency	Roifman syndrome	Immune dysregulation, NOD2 variant	Immune dysregulation	CVID	CGD
COVID-19 test method	RT-PCR	Rapid antigen test	Rapid antigen test	Rapid antigen test + PCR	RT-PCR	Rapid antigen test	RT-PCR	Rapid antigen test	Rapid antigen test	Rapid antigen test
Presenting symptoms	Cough, URI fatigue	Cough, headache, loss of smell and taste, fatigue	Cough, URI	Cough, URI, fatigue	Cough, headache	Fever, cough, URI, fatigue	fever, cough, URI, headache	URI	fever, cough, arthralgia	fever, cough, URI (first infection), Two months later brief URI
Duration of symptoms	3 weeks	2 weeks	1 week	5 days	10 days	NA	1 week	2.5 weeks	3-4 days	3 days, 1-2 days
Other health problems	Asthma	OSA, liver cirrhosis, anemia		Hypothyroidism, global developmental delay	Barter syndrome with renal calcifications, liver cirrhosis, hypersplenism, IBD	Mild asthma, CNS vasculitis, seizures	AIHA, liver cirrhosis, s/p splenectomy	Multiple Sclerosis, ITP, AIHA, Myasthenia Gravis		Hypothyroidism
Chronic treatment and prophylaxis	none	IVIG	IVIG	IVIG	IVIG, Filgrastim, Prednisone, MMF	IVIG	IVIG, Prednisone	IVIG	IVIG	none
Vaccination status	3 doses	3 doses	3 doses	2 doses	3 doses	3 doses	4 doses	3 doses	3 doses	3 doses
COVID-19 treatment	anti-COVID19 mAB (sotrovimab)	Empiric antibiotics, Prednisone	none	none	anti-SARS-CoV-2 mAB (sotrovimab)	Paxlovid	anti-SARS-CoV-2 mAB (sotrovimab)	none	none	none
Follow up (months)	4	6	4	7	4	0.5	6	6	1	2

Note: CID, combined immunodeficiency; CVID, common variable immune deficiency; URI, upper respiratory illness; NA, not available; OSA, obstructive sleep apnea; IBD, inflammatory bowel disease; CGD, chronic granulomatous disease; ITP, idiopathic thrombocytopenic purpura; AIHA, autoimmune hemolytic anemia; MMF, Mycophenolate mofetil; mAB, monoclonal antibodies.

Discussion

We report the clinical manifestations and outcomes of 10 adult patients with IEI. This heterogeneous cohort includes patients with humoral immunodeficiency such as hypogammaglobulinemia, combined immunodeficiency such as DOCK8 deficiency, syndromic immunodeficiency (Roifman syndrome), immune dysregulation disorders, and CGD. All patients had an uncomplicated clinical course without the need for hospital admission, even in those with underlying lung disease.

Compared with previous reports of higher disease severity in IEI patients, a number of protective factors may have contributed to milder disease in our cohort. First, all patients in our cohort were diagnosed with COVID-19 between December 2021–July 2022, a period of predominance of the omicron variant, as opposed to the alpha and delta strains likely impacting patients in earlier reports (Araf et al. 2022). Additionally, 7 of 10 patients had been receiving immunoglobulin replacement, likely providing patients with some degree of passive immunity. It is noteworthy that our center has diligently recommended vaccination against SARS-CoV-2 for all patients with IEI, including those with humoral deficiency. Indeed, while specific antibody responses may be variable in such patients, cellular immunity may still be highly beneficial. Finally, specific treatment with sotrovimab or paxlovid were initiated by community practitioners in 50% of our patients, although it remains unclear whether mild symptoms and disease resolution occurred in these patients due to this treatment. It remains unclear under what circumstances and in which IEI patients this treatment should be administered.

We conclude that patients affected by IEI may show clinical resilience in the face of COVID-19 infection, with vaccination against SARS-CoV-2 and immunoglobulin replacement therapy representing possible protective factors in this patient population. Diligent long-term follow-up studies are warranted and are ongoing to ensure no severe or unique complications develop in this patient population.

REFERENCES

Araf, Y., Akter, F., Tang, Y.-D., Fatemi, R., Parvez, M.S.A., Zheng, C., and Hossain, M.G. 2022. Omicron variant of SARS-CoV-2: genomics, transmissibility, and responses to current COVID-19 vaccines. J. Medical Virol. doi: 10.1002/jmv.27588.

Castano-Jaramillo, L.M., Yamazaki-Nakashimada, M.A., O'Farrill-Romanillos, P.M., Muzquiz Zermeño, D., Mendoza, S.C.S., Montoya, E.V., Campos, J.A.G., Sánchez-Sánchez, L.M., González, L.B.G., López, J.M.R., Ogando, JCB, Vásquez-Echeverri, E., Torres, E.A.M., Lopez-Herrera, G., Galicia, L.B., Ruiz, L.B., Staines-Boone, A.T., Espinosa-Padilla, S.E., Mendez, N.H.S., and Reyes, S.O.L. 2021. COVID-19 in the context of inborn errors of immunity: a case series of 31 patients from Mexico. J. Clin. Immunol. **41**: 1463–1478. PMID: 34114122. doi: 10.1007/s10875-021-01077-5

Cucinotta, D., and Vanelli, M. 2020. WHO declares COVID-19 a pandemic. Acta. Biomedica. **91**: 157–160. doi: 10.23750/abm.v91i1.9397.

Esenboga, S., Ocak, M., Akarsu, A., Bildik, H.N., Cagdas, D., Iskit, A.T., and Tezcan, I. 2021. COVID-19 in patients with primary immunodeficiency. J. Clin. Immunol. **41**, 1515–1522. doi: 10.1007/s10875-021-01065-9.

Giardino, G., Milito, C., Lougaris, V., Punziano, A., Carrabba, M., Cinetto, F., Scarpa, R., Dellepiane, R.M., Ricci, S., Rivalta, B., Conti, F., Marzollo, A., Firinu, D., Cirillo, E., Lagnese, G., Cancrini, C., Martire, B., Danieli, M.G., Pession, A., Vacca, A., Azzari, C., Fabio, G., Soresina, A., Agostini, C., Spadaro, G., Badolato, R., Cicalese, M.P., Aiuti, A., Plebani, A., Quinti, I., and Pignata, C. The impact of SARS-CoV-2 infection in patients with inborn errors of immunity: the experience of the italian primary immunodeficiencies network (IPINet). J. Clin. Immunol. **42**(5): 935–946. PMID: 35445287. doi: 10.1007/s10875-022-01264-y.

Kahn, J.S., and Mcintosh, K. 2005. History and Recent Advances in Coronavirus Discovery. J. Pediatr. Infect. Dis. **24**: S223–S227. PMID: 16378050. doi: 10.1097/01.inf.0000188166.17324.60.

Jin, H., Reed, J.C., Liu, S.T.H., Ho, H-E., Lopes, J.P., Ramsey, N.B., Waqar, O., Rahman, F., Aberg, J.A., Bouvier, N.M., and Cunningham-Rundles, C., and Mount Sinai Health System Convalescent Plasma Team. 2020. Three patients with X-linked agammaglobulinemia hospitalized for COVID-19 improved with convalescent plasma. J. Allergy Clin. Immunol. Pract. **8**: 3594–3596.e3. PMID: 32947026. doi: 10.1016/j.jaip.2020.08.059.

Meyts, I., Bucciol, G., Quinti, I., Neven, B., Fischer, A., Seoane, E., Lopez-Granados, E., Gianelli, C., Robles-

Marhuenda, A., Jeandel, P-Y., Paillard, C., Sankaran, V.G., Demirdag, Y.Y., Lougaris, V., Aiuti, A., Plebani, A., Milito, C., Dalm, V., Guevara-Hoyer, K., Sánchez-Ramón, S., Bezrodnik, L., Barzaghi, F., Gonzalez-Granado, L.I., Hayman, G.R., Uzel, G., Mendonça, L.O., Agostini, C., Spadaro, G., Badolato, R., Soresina, A, Vermeulen, F., Bosteels, C., Lambrecht, B.N., Keller, M., Mustillo, P.J., Abraham, R.S., Gupta, S., Ozen, A., Karakoc-Aydiner, E., Baris, S., Freeman, A.F., Yamazaki-Nakashimada, M., Scheffler-Mendoza, S., Espinosa-Padilla, S., Gennery, A.R., Jolles, S., Espinosa, Y., Poli, M.C., Fieschi, C., Hauck, F., Cunningham-Rundles, C., Mahlaoui, N., IUIS Committee of Inborn Errors of Immunity, Warnatz, K., Sullivan, K.E., and Tangye, S.G. 2021. Coronavirus disease 2019 in patients with inborn errors of immunity: an international study. J. Allergy. Clin. Immunol. **147**: 520–531. PMID: 32980424. doi: 10.1016/j.jaci.2020.09.010.

Shields, A.M., Burns, S.O., Savic, S., and Richter, UK PIN COVID-19 Consortium. 2021. COVID-19 in patients with primary and secondary immunodeficiency: The United Kingdom experience. J. Allergy Clin. Immunol. **147**: 870–875.e1. PMID: 33338534. doi: 10.1016/j.jaci.2020.12.620.

van Damme, K.F.A., Tavernier, S., Roy, N.V., Leeuw, E.D., Declercq, J., Bosteels, C., Maes, B., Bruyne, M.D., Bogaert, D, Bosteels, V., Hoste, L., Naesens, L., Maes, P, Grifoni, A., Weiskopf, D., Sette, A, Depuydt, P., Braeckel, E.V., Haerynck, F, and Lambrecht, B.N. 2020. Case report: convalescent plasma, a targeted therapy for patients with cvid and severe COVID-19. Front. Immunol. **11**: 596761. PMID: 33329586. doi: 10.3389/fimmu.2020.596761.