Immunol Genet J, Vol. 9, No. 1, 2026, pp.26-28 **DOI: https://doi.org/10.18502/igj.v9i1.21885**

Letter to Editor

Treatment of Patients with Inborn Errors of Immunity Should Not Be Postponed until Genetic Confirmation

Saba Fekrvand[1,2], Samanah Abdolahzadeh[3], Marjan Aghajani[4], Mina Ahmadi[5], Mostafa Alavi-Moghaddam[6], Saba Arshi[5], Maryam Asarehzadegan Dezfouli[7], Marzieh Asgharyan[5], Parisa Ashournia[8], Aida Askarisarvestani[9], Raheleh Assari[10,11], Hadi Badiee[12], Sima Bahrami[5], Maryam Behfar[13], Nasrin Behniafard[14], Mahsa Choroom Kheirabadi[4], Zahra Daneshmandi[15], Mohammad Hassan Bemanian[5], Taher Cheraghi[16], Kian Darabi[5], Sepideh Darougar[17], Sarehsadat Ebrahimi[18,19], Golnaz Eslamian[3], Maryam Esmaeilbeig[20], Morteza Fallahpour[5], Nader Faraji[5], Shahin Farzadmanesh[4], Kimiya HajiAbbasi Someesaraie[5], Arash Kalantari[21], Mahdieh Karimizadeh[3], Elham Kaviani[5], Mehrnaz Mesdaghi[3], Majid Marjani[22], Mohammadreza Modaresi[23], Iraj Mohammadzadeh[24, 25], Mahshid Movahedi[4,21], Masoud Movahedi[4], Mohammamd Nabavi[5], Leyla Norouzi-Barough[26], Anahita Razaghian[27,28], Mansoureh Shariat[29], Sahar Seraj[3], Soodeh Seyedi[4], Seyedehshabnam Seyedsalehi[5], Alireza Shafiei[30], Zahra Shahraki Ghadimi[31], Behzad Shakerian[32], Samin Sharafian[3], Sima Shokri[5], Marzieh Tavakol[33], Ahmad Vosughi Motlagh[34], Reza Yazdani[1,2], Nima Rezaei[1,2*]

1 Research Center for Immunodeficiencies, Pediatrics Center of Excellence, Children's Medical Center Hospital, Tehran University of Medical Sciences, Tehran, Iran
2 Primary Immunodeficiency Diseases Network (PIDNet), Universal Scientific Education and Research Network (USERN), Tehran, Iran
3 Department of Allergy and Clinical Immunology, Mofid Children's Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
4 Division of Allergy and Clinical Immunology, Department of Pediatrics, Pediatrics Center of Excellence, Children's Medical Center Hospital, Tehran University of Medical Sciences, Tehran, Iran
5 Department of Allergy and Clinical Immunology, Rasool Akram Hospital, Iran University of Medical Sciences, Tehran, Iran
6 Department of Emergency Medicine, Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
7 Allergy and Clinical Immunology Clinic, AbuRehan Polyclinic, Social Security Organization. Tehran, Iran
8 Department of Allergy and Clinical Immunology, Bahrami Hospital, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
9 Allergy Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
10 Pediatric Rheumatology Research Group, Rheumatology Research Center, Tehran, Iran
11 Department of Pediatrics, Pediatrics Center of Excellence, Children's Medical Center Hospital, Tehran University of Medical Sciences, Tehran, Iran
12 Shahid Beheshti University of Medical Sciences, Tehran, Iran
13 Pediatric Cell and Gene Therapy Research Centre, Gene, Cell & Tissue Research Institute, Tehran University of Medical Sciences, Tehran, Iran
14 Children Growth Disorder Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
15 Pediatric Respiratory Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran
16 Department of Pediatrics, 17th Shahrivar Children's Hospital, Guilan University of Medical Sciences, Rasht, Iran
17 Department of Pediatrics, Faculty of Medicine, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran
18 Department of Immunology and Allergy, Kerman University of Medical Sciences, Kerman, Iran
19 Endocrinology and Metabolism Research Center, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran
20 Department of Allergy and Clinical Immunology, Shiraz University of Medical Sciences, Shiraz, Iran
21 Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran
22 Clinical Tuberculosis and Epidemiology Research Center, National Research Institute of Tuberculosis and Lung Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran
23 Pediatric Pulmonary Disease and Sleep Medicine Research Center, Pediatric Center of Excellence, Children's Medical Center Hospital, Tehran University of Medical Sciences, Tehran, Iran
24 Non-communicable Pediatric Diseases Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran
25 USERN Office, Babol University of Medical Sciences, Babol, Iran
26 Immunodeficiency Diseases Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
27 Department of Allergy and Clinical Immunology, Hakim Children's Hospital, Tehran University of Medical Sciences, Tehran, Iran
28 Immunology, Allergy and Asthma Research Institute, Tehran University of Medical Sciences, Tehran, Iran
29 Department of Immunology and Allergy, Children's Medical Center Hospital, Tehran University of Medical Sciences, Tehran, Iran
30 Department of Allergy and Immunology, Bahrami Children's Hospital, Tehran University of Medical Sciences, Tehran, Iran
31 Department of Pediatrics, Clinical Immunology Research Center, Zahedan University of Medical Sciences, Zahedan, Iran
32 Department of Immunology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
33 Non-Communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran
34 Department of Pediatrics, North Khorasan University of Medical Sciences, Bojnurd, Iran

Received: 16 November 2025; Accepted: 11 February 2026

***Corresponding Author:** Nima Rezaei, MD, PhD
Research Center for Immunodeficiencies, Pediatrics Center of Excellence, Children's Medical Center Hospital, Tehran University of Medical Sciences, Tehran, Iran
E-mail: rezaei_nima@yahoo.com

How to cite this article
Fekrvand S, Abdolahzadeh S, Aghajani M, Ahmadi M, Alavi-Moghaddam M, Arshi S, et al. Treatment of Patients with Inborn Errors of Immunity Should Not Be Postponed until Genetic Confirmation. Immunol Genet J, 2026; 9(1): 26-28 DOI: https://doi.org/10.18502/igj.v9i1.21885

Introduction

Inborn errors of immunity (IEIs) are a heterogeneous group of more than 500 genetically inherited disorders with impaired innate and/or adaptive immune system (1, 2). The optimal therapeutic approach varies depending on the affected component of the immune system (3). The patients' susceptibility to recurrent infections could lead to life-threatening complications as well as decreased quality of life of these patients, if left untreated (4). Therefore, timely initiation of the appropriate management based on clinical presentation and immunological evaluation is essential, as delaying management until genetic confirmation can result in irreversible complications particularly in underdeveloped and developing countries, where Whole-Exome Sequencing (WES) are still quite expensive, not always available, and may require prolonged processing times (5). Below, we review 3 important IEI phenotypes for which immediate treatment is critical are mentioned as examples.

1. Hypogammaglobulinemias

Hypogammaglobulinemias represent a group of IEIs characterized by impaired humoral immunity, thus decreased serum levels of immunoglobulins (6). This condition predisposes the patients to various and severe infections, pulmonary complications, autoimmunity, lymphoproliferation and malignancy (6). The diagnosis typically relies on clinical features combined with significant decrease in IgG levels (5, 7). Although various genes are involved in pathogenesis of hypogammaglobulinemias (8), the management approach is uniform across genetic subtypes including prevention through antimicrobial prophylaxis and immunoglobulin replacement therapy, either intravenous (IvIg) or subcutaneous (ScIg), which must be initiated promptly after clinical and immunological diagnosis (4). Our recent national consensus guideline on diagnosis and management of predominantly antibody deficiencies comprehensively describes management strategies for these patients (9).

2. Congenital Neutropenias

Congenital neutropenias are a group of IEIs characterized by reduced neutrophil counts, thus susceptibility to mucocutaneous infections, abscess and invasive bacterial disease (10, 11). The diagnosis is based on clinical manifestations along with absolute neutrophil count (ANC) below 1500 cells/μl (5, 11, 12), while severe neutropenia is considered for ANC of less than 500 cells/μl. Although various genetic defects may be involved, the mainstay of therapy for congenital neutropenia, especially once the maturation arrest at preliminary stages of differentiation of myeloid series is confirmed in the bone marrow, consists of antimicrobial prevention and treatment of infections as well as administration of recombinant granulocyte colony-stimulating factor (G-CSF) (11, 12). G-CSF promotes development and function of neutrophils, significantly lowering the risk of life-threatening infections and improving survival in these patients (11, 12). Treatment should begin immediately upon confirming congenital neutropenia, after exclusion of other causes of neutropenia, without waiting for genetic results (11, 12). Detailed recommendations on management of these patients are outlined in our recent national consensus guideline on diagnosis and management of congenital neutropenias (13).

3. Chronic Granulomatous Disease (CGD)

CGD is another group of IEIs with defects in respiratory burst of phagocytes due to mutations in genes encoding components of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex that predispose the affected patients to recurrent invasive bacterial and fungal infections and inflammatory complications (14, 15). The diagnosis relies on clinical findings along with absent/significantly decreased respiratory burst activity, confirmed by dihydrorodamine (DHR) assays or nitroblue tetrazolium (NBT) (if the first one was not available) (5, 15). Prevention of these infections through early initiation of antibacterial and antifungal prophylaxis together with administration of immunomodulatory therapy with interferon gamma (IFN-γ), especially in the X-linked form due to mutation of CYBB, is the cornerstone of management of these patients (16). IFN-γ acts by enhancing the oxidative burst, thus phagocytes' bacterial-killing activity (17). These treatments should start at the earliest time

after making diagnosis of CGD, based on the clinical and immunological data; and there is no need to wait to have the genetic diagnosis (16). The detailed management approach of these patients is provided in our recently published national consensus guideline on diagnosis and management of CGD (18).

In conclusion, timely implementation of therapeutic measures following clinical and immunological diagnosis of IEIs is life-saving and should not be delayed pending genetic confirmation. Early therapeutic intervention prevents irreversible organ damage, reduces mortality, and improves long-term outcomes, particularly in settings where genetic testing is costly or not rapidly accessible.

References

1. Bousfiha AA, Jeddane L, Moundir A, Poli MC, Aksentijevich I, Cunningham-Rundles C, et al. The 2024 update of IUIS phenotypic classification of human inborn errors of immunity. J Hum Immun. 2025;1(1):e20250002.
2. Rezaei N SM, de Vries E, Bousfiha AA, Orange J, Puck J. Introduction on inborn errors of immunity. In Rezaei N, ed. Inborn errors of immunity: definition, diagnosis, and management. Springer Nature, Switzerland 2025. 1-120.
3. Abolhassani H, Avcin T, Bahceciler N, Balashov D, Bata Z, Bataneant M, et al. Care of patients with inborn errors of immunity in thirty J Project countries between 2004 and 2021. Front Immunol. 2022;13:1032358.
4. Pimenta F, Palma SMU, Constantino-Silva RN, Grumach AS. Hypogammaglobulinemia: a diagnosis that must not be overlooked. Braz J Med Biol Res. 2019;52(10):e8926.
5. Grumach AS, Goudouris ES. Inborn Errors of Immunity: how to diagnose them? Jornal de Pediatria. 2021;97.
6. dos Santos Vilela MM. Human Inborn Errors of Immunity (HIEI): predominantly antibody deficiencies (PADs): if you suspect it, you can detect it. Jornal de Pediatria. 2021;97:S67-S74.
7. Conley ME, Notarangelo LD, Etzioni A. Diagnostic criteria for primary immunodeficiencies. Representing PAGID (Pan-American Group for Immunodeficiency) and ESID (European Society for Immunodeficiencies). Clin Immunol. 1999;93(3):190-7.
8. Conley ME. Genetics of hypogammaglobulinemia: what do we really know? Curr Opin Immunol. 2009;21(5):466-71.
9. Reza Y, Samaneh A, Parisa A, Aida A, Sima B, Maryam B, et al. National Consensus Guideline on Diagnosis and Management of Predominantly Antibody Deficiencies. Immunology and Genetics Journal. 2024;7(2).
10. Donadieu J, Beaupain B, Fenneteau O, Bellanne-Chantelot C. Congenital neutropenia in the era of genomics: classification, diagnosis, and natural history. Br J Haematol. 2017;179(4):557-74.
11. Min KI, Byeon S. Diagnosis and management of neutropenia. Blood Res. 2025;60(1):30.
12. Donadieu J, Fenneteau O, Beaupain B, Mahlaoui N, Chantelot CB. Congenital neutropenia: diagnosis, molecular bases and patient management. Orphanet J Rare Dis. 2011;6(1):26.
13. Fekrvand S, Yazdani R, Abdolahzade S, Ashournia P, Askarisarvestani A, Bahrami S, et al. National Consensus Guideline on Diagnosis and Management of Congenital Neutropenias. Immunology and Genetics Journal. 2024.
14. Song E, Jaishankar GB, Saleh H, Jithpratuck W, Sahni R, Krishnaswamy G. Chronic granulomatous disease: a review of the infectious and inflammatory complications. Clin Mol Allergy. 2011;9(1):10.
15. Staudacher O, von Bernuth H. Clinical presentation, diagnosis, and treatment of chronic granulomatous disease. Front Pediatr. 2024;12:1384550.
16. Justiz-Vaillant AA, Williams-Persad AF, Arozarena-Fundora R, Gopaul D, Soodeen S, Asin-Milan O, et al. Chronic Granulomatous Disease (CGD): Commonly Associated Pathogens, Diagnosis and Treatment. Microorganisms. 2023;11(9):2233.
17. Lugo Reyes SO, Gonzalez Garay A, Gonzalez Bobadilla NY, Rivera Lizarraga DA, Madrigal Paz AC, Medina-Torres EA, et al. Efficacy and Safety of Interferon-Gamma in Chronic Granulomatous Disease: a Systematic Review and Meta-analysis. J Clin Immunol. 2023;43(3):578-84.
18. Delavari S, Yazdani R, Abolhassani H, Salami F, Ashournia P, Askarisarvestani A, et al. National Consensus Guideline on Diagnosis and Management of Chronic Granulomatous Disease. Immunol Genet J. 2025;8(3):258-266.