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Review Article

National Consensus Guideline on Diagnosis and Management of Congenital Neutropenias

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Abstract

At present, a national consensus or guideline for diagnosing and managing patients suspected of having severe congenital neutropenia (SCN) is lacking. This consensus is written based on a combination of scientific literature and comments from the expert panel of Iranian immunologists. A group of clinical immunologists reviewed the current consensus, presented their comments at a meeting titled "First Meeting on the Diagnosis of Inborn Errors of Immunity (IEI) by IEI Experts" and agreed on this consensus. This consensus guideline provides recommendations on the diagnosis, antimicrobial prophylaxis, management of clinical manifestations, administration of granulocyte colony-stimulating factor (G-CSF) and hematopoietic stem cell transplantation (HSCT) for patients with SCN.

Keywords: National Consensus; Inborn Errors of Immunity; Severe Congenital Neutropenia; Management; G-CSF; HSCT.

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Introduction

Inborn errors of immunity (IEI), previously known as primary immunodeficiencies (PID) are a heterogenous group of congenitally inherited disorders with defects in one or more components of innate and/or adaptive immune system (1). To date, approximately 500 IEI diseases have been found based on the affected immune system components (1).

Congenital neutropenias are a heterogeneous group of IEI that belong to the phagocytic defects category of IEI classification proposed by the International Union of Immunological Societies (IUIS) (2) and are characterized by three main features including low neutrophil count and susceptibility to infection, various organ dysfunctions, and an extraordinarily high risk of leukemic transformation (3). Congenital neutropenia is an extraordinarily rare condition with an approximate prevalence of less than 1:100,000 worldwide (4). Congenital neutropenias range from isolated severe congenital neutropenia (SCN) to complex inherited disorders affecting other organ systems comprising intellectual disabilities, pancreatic insufficiency, metabolic disease, facial dysmorphias or skin hypopigmentation (5). In **Table 1**, we have precisely represented various genes associated with congenital neutropenia and their accompanying features.

Severe neutropenia in SCN rises from bone marrow maturation arrest in the myeloid series (5). Affected patients manifest a variety of clinical features including recurrent bacterial infections of skin and mucosal linings of oropharynx, oral aphthae, periodontitis, gingivitis and dental decay, skin abscess, upper and lower respiratory tract infections, as well as cognitive and neurological defects in some patients (6-8). Mutations in *ELANE* gene encoding neutrophil elastase, a serine protease destroying microorganisms and breaking down local tissue during inflammation, account for more than half of SCN cases (9, 10). The mainstay of therapy for SCN is prevention of infections through antimicrobial prophylaxis and administration of recombinant human granulocyte colony-stimulating factor (G-CSF) and hematopoietic stem cell transplantation (HSCT) in unresponsive or severe cases (6).

The aim of current national consensus is to provide a comprehensive review for diagnosing, management and therapeutic challenges of SCN patients based on a combination of scientific literature and the comments of the expert panel of Iranian clinical immunologists.

Consensus on Diagnosis of SCN

Neutropenia is defined as an absolute neutrophil count (ANC) below 1500/mm^3 and is considered mild in case of 1000/mm^3 < ANC < 1500/mm^3, moderate in case of 500/mm^3 < ANC < 1000/mm^3 and severe in case of ANC < 500/mm^3.

Diagnosis of congenital neutropenia is made based on the diagnostic criteria for IEI recommended by European Society for Immunodeficiencies (ESID) including neutropenia below 0.5 g/L (in at least triple measurement) or neutropenia below 1 g/L measured on at least 3 occasions with at least one of the following: deep seated infection due to bacteria and/or fungi, recurrent pneumonia, buccal and/or genital aphtous lesions or ulcerations, omphalitis or affected family member along with exclusion of secondary causes of neutropenia (https://esid.org/Working-Parties/Registry-Working-Party/Diagnosis-criteria).

Consensus Recommendations and Discussion on Antimicrobial Prophylaxis

The most suitable antimicrobial prophylaxis for prevention of recurrent infections in SCN patients is antimicrobial chemoprophylaxis with daily oral sulfamethoxazole/trimethoprim combination (Bactrim®) at a dose of 50 mg/kg (11). Complete prevention of gingivostomatitis in SCN patients is made through concurrent therapy with sulfamethoxazole/trimethoprim combination and metronidazole that is active on the oral saprophytic flora, particularly anaerobes (11).

Consensus Recommendations and Discussion on Management of Clinical Manifestations in SCN

In the following sections we have discussed management of the most important clinical complications in SCN patients.

Acute Infectious Episodes

Superficial or ENT infections could be managed by oral antibiotic therapy alongside regular monitoring of inflammatory markers (11). In

case of sepsis in SCN patients, they should immediately be hospitalized with prompt initiation of parenteral antibiotic therapy including a combination of a third-generation cephalosporin and an aminoside (12). There is controversy regarding placing of glycopeptides (vancomycin and teicoplanin) in first-line therapy (6). Antifungal treatment should be added in case of fever persisting beyond 5 days (13). G-CSF administration should be started in critical cases, either at a dose to which the patient is known to respond, or at the standard dose of 5 μg/kg/day or a higher dose if no improvement is observed (12).

Extra-Hematopoietic Involvement

The most devastating extra-hematopoietic involvement in some of patients with SCN, particularly those with HCLS1-associated protein X-1 (HAX1) deficiency is neurodegenerative processes, which has no curative treatment to date (6, 11).

Table 1. Classification of congenital neutropenias, their associated features, and affected gene.

Associated features with congenital neutropenia	IEI	Affected gene	Inheritance
Isolated congenital neutropenia	Elastase deficiency	*ELANE*	AD
	G-CSF receptor deficiency	*CSF3R*	AR
	CXCR2 deficiency	*CXCR2*	AR
	X-linked neutropenia/myelodysplasia	*WAS*	XL GOF
Oculocutaneous hypopigmentation	Chediak-Higashi syndrome	*LYST*	AR
	Griscelli syndrome, type 2	*RAB27A*	AR
	Hermansky-Pudlak syndrome, type 2	*AP3B1*	AR
	P14/LAMTOR2 deficiency	*LAMTOR2*	AR
Pancreatic insufficiency	Shwachman-Diamond Syndrome	*SBDS*, *DNAJC21*, *EFL1*	AR
	SRP54 deficiency	*SRP54*	AD
Metabolic disease	Glycogen storage disease type 1b	*G6PT1*	AR
Neurological defect	HAX1 deficiency (Kostmann Disease)	*HAX1*	AR
	3-Methylglutaconic aciduria	*CLPB*	AR
Dysmorphism	Cohen syndrome	*VPS13B*	AR
	Clericuzio syndrome (Poikiloderma with neutropenia)	*USB1*	AR
Renal disease	VPS45 deficiency	*VPS45*	AR
Cardiopathy	Barth Syndrome (3-Methylglutaconic aciduria type II)	*TAZ*	XL
	G6PC3 deficiency	*G6PC3*	AR
Bone defect	JAGN1 deficiency	*JAGN1*	AR
	SMARCD2 deficiency	*SMARCD2*	AR
Bilobed nuclei neutrophils	Specific granule deficiency	*CEBPE*	AR
Bone marrow insufficiency	Dyskeratosis congenita	*DKC1*, *TERC*, *TERT*, *TINF2*, *RTEL1*, *ACD*, *NOLA3*, *NOLA2*, *WRAP53*, *PARN*	AR, AD, XL
	GATA2 deficiency	*GATA2*	AD
	Fanconi anemia	*FANCA*, *FANCB*, *FANCC*, *BRCA2*, *FANCD2*, *FANCE*, *FANCF*, *XRCC9*, *FANCI*, *BRIP1*, *FANCL*, *FANCM*, *PALB2*, *RAD51C*, *SLX4*, *ERCC4*, *RAD51*, *BRCA1*, *UBE2T*, *XRCC2*, *MAD2L2*, *RFWD3*	AR, XLR
Immunodeficiency	WHIM (Warts, Hypogammaglobulinemia, Infections, Myelokathexis) syndrome	*CXCR4*	AD GOF
	Reticular dysgenesis	*AK2*	AR
	CD40 ligand (CD154) deficiency	*CD40LG*	XL

IEI, inborn errors of immunity; AD, autosomal dominant; AR, autosomal recessive; XL, X-linked; GOF, gain of function; XLR, X-Linked recessive.

Malignant Transformation

Congenital neutropenia is a preleukemic state with cumulative incidence of leukemia being approximately 15% at age 20 years among SCN patients (14). Patients with underlying mutations in *ELANE*, *HAX1, WASP, SBDS* and *G6PC3* or *SLC37A4* are found to experience leukemic transformation (14-20). The severity of neutropenia, and the use of G-CSF, especially at high doses (> 15 µg/kg/day) and for long periods are known as the main risk factors for leukemic onset due to hyperstimulation of the monocyte lineage, which may warrant HSCT in these patients (14, 21, 22).

Consensus Recommendations and Discussion on G-CSF

Susceptibility to bacterial infections and sepsis in patients with SCN is due to absence or deficit of neutrophil granulocytes (5). In this regard, administration of G-CSF serves as a key part of therapeutic management in these patients through promotion of development and function of neutrophils (5). G-CSF has improved survival and quality of life of SCN patients (12, 23). Lenograstim and filograstim are the currently available two forms of G-CSF in clinical use (24). Peg-Filgrastim, a commercially available pegylated form of G-CSF and a combination of filgrastim and polyethylene glycol, has a longer half-life of 15 to 80 hours with lower required numbers of injections; however, is not routinely used in SCN patients (25).

The induction phase of G-CSF treatment should be initiated at a dose of 3-5 µg/kg body weight given subcutaneously every other day (11, 13). Changes in the neutrophil count should be serially followed through blood cell counts to evaluate response to G-CSF that is defined as a rise in the neutrophil count (> 1.5 G/l) and the clinical improvement by reduction in frequency of infectious episodes, after 10 to 15 days (11, 13). In case of no response after a period of 15 days, the daily dose should be increased in steps of 5 µg/kg (11, 13). Contrarily, the dose should be halved in case of rapid or even excessive response (PN > 5 G/l)(11, 13). After determining the minimal daily dose, the maintenance phase can initiate aiming to determine the minimal dose and injection rhythm for sustaining a clinical response with blood count monitoring every 4 to 6 months (11, 13). Splenomegaly, thrombocytopenia, osteopenia, osteoporosis, flu-like reactions, bone pain, vasculitis, skin rashes and most importantly malignant development to myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) have been reported among side effects of G-CSF (26, 27).

Consensus Recommendations and Discussion on HSCT

Currently, absolute indications for HSCT are patients who fail to respond to G-CSF (>50 µg/kg/day) or those developing MDS/leukemia (5, 6, 21, 28, 29) with respectively 89% and 75% combined overall and event free survival (EFS) in those undergoing HSCT without malignant transformation (30). Moreover, there are controversial recommendations on indication for HSCT in high-risk patients including those requiring high doses of G-CSF (>8 µg/kg/day), harboring G-CSF receptor mutations or those with the Gly185Arg mutation in the *ELANE* gene (5, 6). In the future with improvements in molecular HLA-typing and donor selection, prevention of graft-versus host disease (GVHD) and supportive care, HSCT might be recommended even for SCN patients not meeting the abovementioned criteria (31).

Consensus Recommendations and Discussion on Daily Life of SCN Patients

SCN patients should be educated to regularly follow preventive measures, most importantly oral and skin hygiene as well as annual dental checkup (11).

Intramuscular injections and rectal temperature measurement may be harmful and should be avoided as much as possible (11).

No dietary restrictions are required in SCN patients (11).

Deprivation of SCN patients from social interaction is not necessary as they are not usually susceptible to viral epidemics (11).

Conclusions

Herein, we have provided the first national consensus guideline on the diagnosis and management of SCN patients in Iran in light of scientific literature and comments from the expert

panel of Iranian clinical immunologists. This national consensus guideline could be used as a reference for increasing the awareness of clinicians and improving diagnosis and management of patients with SCN.

Conflict of Interests

There is no conflict of interest.

References

1. Tangye SG, Al-Herz W, Bousfiha A, Cunningham-Rundles C, Franco JL, Holland SM, et al. Human inborn errors of immunity: 2022 update on the classification from the international union of immunological societies expert committee. Journal of clinical immunology. 2022;42(7):1473-507.
2. Bousfiha A, Moundir A, Tangye SG, Picard C, Jeddane L, Al-Herz W, et al. The 2022 update of IUIS phenotypical classification for human inborn errors of immunity. Journal of clinical immunology. 2022;42(7):1508-20.
3. Donadieu J, Beaupain B, Fenneteau O, Bellanné-Chantelot C. Congenital neutropenia in the era of genomics: classification, diagnosis, and natural history. British Journal of Haematology. 2017;179(4):557-74.
4. Donadieu J, Beaupain B, Mahlaoui N, Bellanné-Chantelot C. Epidemiology of congenital neutropenia. Hematology/Oncology Clinics. 2013;27(1):1-17.
5. Spoor J, Farajifard H, Rezaei N. Congenital neutropenia and primary immunodeficiency diseases. Critical Reviews in Oncology/Hematology. 2019;133:149-62.
6. Klein C. Congenital neutropenia. Stiehm's Immune Deficiencies. 2020:797-812.
7. Lebel A, Yacobovich J, Krasnov T, Koren A, Levin C, Kaplinsky C, et al. Genetic analysis and clinical picture of severe congenital neutropenia in Israel. Pediatric Blood & Cancer. 2015;62(1):103-8.
8. Bartocci A, Laino D, Di Cara G, Verrotti A. Epilepsy in Kostmann syndrome: report of a case and review of the literature. Acta Neurologica Belgica. 2016;116:359-62.
9. Boztug K, Klein C. Genetic etiologies of severe congenital neutropenia. Current opinion in pediatrics. 2011;23(1):21-6.
10. Germeshausen M, Deerberg S, Peter Y, Reimer C, Kratz CP, Ballmaier M. The spectrum of ELANE mutations and their implications in severe congenital and cyclic neutropenia. Human mutation. 2013;34(6):905-14.
11. Donadieu J, Fenneteau O, Beaupain B, Mahlaoui N, Chantelot CB. Congenital neutropenia: diagnosis, molecular bases and patient management. Orphanet journal of rare diseases. 2011;6:1-28.
12. Salehi T, Fazlollahi MR, Maddah M, Nayebpour M, Yazdi MT, Alizadeh Z, et al. Prevention and control of infections in patients with severe congenital neutropenia; a follow up study. Iranian Journal of Allergy, Asthma and Immunology. 2012:51-6.
13. Donadieu J, Boutard P, Bernatowska E, Tchernia G, Couillaud G, Philippe N, et al. A European phase II study of recombinant human granulocyte colony-stimulating factor (lenograstim) in the treatment of severe chronic neutropenia in children. European journal of pediatrics. 1997;156:693-700.
14. Donadieu J, Leblanc T, Meunier BB, Barkaoui M, Fenneteau O, Bertrand Y, et al. Analysis of risk factors for myelodysplasias, leukemias and death from infection among patients with congenital neutropenia. Experience of the French Severe Chronic Neutropenia Study Group. haematologica. 2005;90(1):45-53.
15. Rosenberg PS, Alter BP, Link DC, Stein S, Rodger E, Bolyard AA, et al. Neutrophil elastase mutations and risk of leukaemia in severe congenital neutropenia. British journal of haematology. 2008;140(2):210-3.
16. Yetgin S, Olcay L, Koc A, Germeshausen M. Transformation of severe congenital neutropenia to early acute lymphoblastic leukemia in a patient with HAX1 mutation and without G-CSF administration or receptor mutation. Leukemia. 2008;22(9):1797-.
17. Dror Y. Shwachman-Diamond syndrome. Pediatric blood & cancer. 2005;45(7):892-901.
18. Schroeder T, Hildebrandt B, Mayatepek E, Germing U, Haas R. A patient with glycogen storage disease type Ib presenting with acute myeloid leukemia (AML) bearing monosomy 7 and translocation t (3; 8)(q26; q24) after 14 years of treatment with granulocyte colony-stimulating factor (G-CSF): a case report. Journal of Medical Case Reports. 2008;2:1-5.
19. Pinsk M, Burzynski J, Yhap M, Fraser RB, Cummings B, Ste-Marie M. Acute myelogenous leukemia and glycogen storage disease 1b. Journal of pediatric hematology/oncology. 2002;24(9):756-8.
20. Beel K, Vandenberghe P. G-CSF receptor (CSF3R) mutations in X-linked neutropenia evolving to acute myeloid leukemia or myelodysplasia. haematologica. 2009;94(10):1449.
21. Ferry C, Ouachee M, Leblanc T, Michel G, Notz-Carrere A, Tabrizi R, et al. Hematopoietic stem cell transplantation in severe congenital neu-

tropenia: experience of the French SCN register. Bone marrow transplantation. 2005;35(1):45-50.
22. Rosenberg PS, Alter BP, Bolyard AA, Bonilla MA, Boxer LA, Cham B, et al. The incidence of leukemia and mortality from sepsis in patients with severe congenital neutropenia receiving long-term G-CSF therapy. Blood. 2006;107(12):4628-35.
23. Zeidler C, Welte K, editors. Hematopoietic growth factors for the treatment of inherited cytopenias. Seminars in hematology; 2007: Elsevier.
24. Welte K, Gabrilove J, Bronchud MH, Platzer E, Morstyn G. Filgrastim (r-metHuG-CSF): the first 10 years. 1996.
25. Fioredda F, Calvillo M, Lanciotti M, Lanza T, Giunti L, Castagnola E, et al. Pegfilgrastim in children with severe congenital neutropenia. Pediatric Blood & Cancer. 2010;54(3):465-7.
26. James R, Kinsey S. The investigation and management of chronic neutropenia in children. Archives of disease in childhood. 2006;91(10):852-8.
27. Cottle TE, Fier CJ, Donadieu J, Kinsey SE, editors. Risk and benefit of treatment of severe chronic neutropenia with granulocyte colony-stimulating factor. Seminars in hematology; 2002: Elsevier.
28. Oshima K, Hanada R, Kobayashi R, Kato K, Nagatoshi Y, Tabuchi K, et al. Hematopoietic stem cell transplantation in patients with severe congenital neutropenia: an analysis of 18 Japanese cases. Pediatric transplantation. 2010;14(5):657-63.
29. Zeidler C, Welte K, Barak Y, Barriga F, Bolyard A, Boxer L, et al. Stem cell transplantation in patients with severe congenital neutropenia without evidence of leukemic transformation. Blood, The Journal of the American Society of Hematology. 2000;95(4):1195-8.
30. Connelly JA, Choi SW, Levine JE. Hematopoietic stem cell transplantation for severe congenital neutropenia. Current opinion in hematology. 2012;19(1):44-51.
31. Choi SW, Levine JE. Indications for hematopoietic cell transplantation for children with severe congenital neutropenia. 2010.