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REVIEW

CD40 Ligand Deficiency

L.F.B. Leite[a], T.A. Máximo[a], T. Mosca[b], W.C.N. Forte[b,*]

[a] *Immunodeficiency and Allergy Unit - Pediatrics Department, Irmandade da Santa Casa de Misericódia de São Paulo, São Paulo/SP, Brazil*
[b] *Immunology Discipline - Pathology Department, Santa Casa de Sao Paulo School of Medical Sciences, São Paulo/SP, Brazil*

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Abstract CD40 ligand deficiency (CD40L), currently classified as an inborn error of immunity affecting cellular and humoral immunity, prevalently emerges in boys within the first two years of life. It manifests itself as a decrease in serum IgG, IgA and IgE, with normal or high IgM, defects in T cell proliferation, and decrease in soluble CD40L. These accompany sinopulmonary and/or gastrointestinal infections, and there may be infections caused by pyogenic bacteria, opportunistic infections, autoimmune diseases, and neoplasms. Mild and moderate cases of this deficiency may respond well to prophylactic antibiotic therapy or to human immunoglobulin replacement therapy, in addition to the early treatment of infections. Severe cases can be treated with hematopoietic stem cell transplantation, which allows the healing of such patients, rather than sequelae and a poor progression. Thus, its differential diagnosis with other inborn errors of immunity is essential, especially CD40 deficiency and variable common immunodeficiency; the reason why we have proposed the present literature review.

Introduction

The term Primary Immunodeficiency is currently being replaced by Inborn Errors of Immunity, in analogy to the term Inborn Errors of Metabolism.[1] This new classification divides the immunodeficiencies into large groups: immunodeficiencies affecting cellular and humoral immunity, Primary Immunodeficiencies associated to genetic syndromes, predominantly antibody deficiencies, diseases of immune dysregulation, defects of phagocytes, innate immune defects, autoinflammatory diseases, complement deficiencies, phenocopies of Primary Immunodeficiencies.[1]

CD40 ligand deficiency (CD40L), formerly referred to as X-linked hyper-IgM syndrome, is characterized by an immunoglobulin class-switch recombination defect. The result is IgG, IgA and IgE deficiencies, with preserved or elevated IgM values. The disease predominantly affects the male gender, from childhood. It manifests itself mainly due to repeat infections of the respiratory and digestive systems, especially recurrent pneumonias and chronic diarrhea.[2,3]

CD40L deficiency may initially exhibit some similarities with CD40 deficiency and hyper-IgM syndrome. This syndrome was first described by Rosen and Burtin in 1961; its incidence is estimated at 1/500,000 births.[4–6] Genetic

* Corresponding author.
E-mail address: imunosantacasa@gmail.com (W.C.N. Forte).

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alterations in CD40L deficiency may result from mutations that determine defects restricted to the functionality of B lymphocytes or mutations that, in addition to B cells, also affect T cells, monocytes, macrophages, dendritic cells and neutrophils.[1] In addition to genetic causes, immunodeficiencies with an increase in IgM and a decrease in other immunoglobulins were described as secondary to congenital rubella, B-cell leukemia, lymphomas, phenytoin use, and splenectomy.[7]

CD40L deficiency accounts for about 70 % of all cases of immunodeficiencies with increased IgM.[8] Deficiencies with an increase in IgM and decrease in other immunoglobulins may result from changes in different genes encoding: CD40L, CD40, activation-induced cytidine deaminase (AID), NF-κB essential modulator (NEMO), uracil nucleoside glycosylase (UNG — an enzyme involved in nucleic acid coding).[2] Currently CD40L and CD40 deficiencies are classified as Inborn Errors of Immunity that affect cellular and humoral immunity (since they affect the interaction between T and B lymphocytes), whereas the others are predominantly antibody deficiencies (impairment of B functionality).[1]

Following the mutation of CD40L, the most described mutations of these deficiencies are those in the AID-encoding genes: in B-cells, there is a disorder genetic in the recombination encoding IgG, IgA and IgE the heavy chains.[6,9–13] Next there is a mutation in the NEMO gene, encoder NF-κB (B-cell nuclear factor kappa), which upon activation by CD40 participates in the signaling for immunoglobulin class switch. In such cases, in addition to repetitive infections, there may be ectodermal dysplasia, conical teeth and alopecia.[6,10,14,15] Immunodeficiencies with increased IgM caused by mutations in the CD40 molecule are rare and prevent B cells from receiving the cooperation of T cells for class switch. It may result from somatic hypermutations without a perfect definition of molecular alteration.[5,6,9,10,16,17]

Defects in recombination of class-switch, especially those arising from mutations in AID and UNG, respond well to human immunoglobulin replacement therapy.[11,18,19] On the other hand, CD40L deficiency, in moderate to severe cases, does not respond to treatment involving prophylactic antibiotic therapy or human immunoglobulin, sometimes requiring hematopoietic stem cell transplantation. This is one of the main reasons underlying the need to diagnose CD40L deficiency, which assists one to differentiate it from other forms of hyper-IgM syndromes and Inborn Errors of Immunity.

Purpose

The present study aims to review the CD40 ligand deficiency for its inclusion in the differential diagnosis of other inborn errors of immunity.

Methods

Bibliographic review in the PubMed, LILACS and SCIELO database entries up to 2019 using the terms: Immunologic Deficiency Syndromes; CD40 Ligand; Hyper-IgM; Immune System Diseases; Immunoglobulins.

Review results

Pathogeny

The gene responsible for X-linked hyper-IgM syndrome was mapped to the X chromosome (Xq26-27) and subsequently identified as CD40L, expressed on activated $CD4^+$ T lymphocytes.[1,20–24] CD40L, also referred to as TNFSF5 or CD154, is a Type II transmembrane protein, expressed on the cell surface as a trimer. It acts as a co-stimulatory molecule, influencing the function of CD40-expressing cells: B lymphocytes, macrophages, dendritic cells, activated $CD8^+$ T lymphocytes, and other cells not directly related to immune response.[25]

CD40L-CD40 binding in B cells causes immunoglobulin class switch: there is a genetic rearrangement of the VDJ segments (variable - V; diversity - D; joining - J) that encode the heavy chains of the immunoglobulin molecule, resulting in class switch from IgM to IgG or IgA or IgE, depending on the type of cytokine produced by the $CD4^+$ T lymphocyte. Without the CD40L-CD40 binding, B lymphocytes cannot undergo class switch and will produce only class M (IgM) antibodies, with a consequent decrease in serum IgG, IgA and IgE.[26,27] In addition to this somatic rearrangement, there is a hypermutation, especially in the variable segments, which results in a great diversity of antibodies. B lymphocyte development and antibody diversity generation are said to occur independently of the antigen interacting with lymphocyte CD40L binding to T. The interaction between T and B lymphocytes is based on the direct contact between cells and the presence of soluble factors, such as cytokines, and plays a key role in antibody response maturation. Among the interactions involving cell membranes, CD40L-CD40 binding is critical for class switching, for the survival of differentiated B lymphocytes in plasma cells and memory cells, and for suppressing apoptosis in these cells.[8,26] The CD40L-CD40 interaction can also affect other cells, increasing cytokine and chemokine synthesis, the expression of other costimulatory molecules and adhesion molecules involved in the inflammatory response and clonal expansion of B, thereby preventing B apoptosis in germinal centers.[27]

For these reasons, the explanation for the increased susceptibility of CD40L deficiency to infections, in addition to reduced immunoglobulin synthesis, is given by the pleiotropic role of the CD40L-CD40 interaction in the regulation of the immune response.

Transient and/or chronic neutropenia, abnormalities of cell differentiation, T cell abnormalities and decreased interferon-gamma synthesis (IFN-γ) may also be present in the CD40L deficiency.[14,17,28,29]

Clinical presentation

In the classic clinical of CD40L deficiency, the manifestations almost always appear in boys during the first two years of life, with infectious processes dependent on exposure to pathogens and local epidemiology.[14,15]

The clinical diagnosis of CD40L deficiency is based on at least one of the following criteria: an increased susceptibility to infections (repeat and/or opportunistic infections, including *Cryptosporidium parvum*); immune dysregulation

(autoimmune diseases, lymphoproliferative or sclerosing cholangitis); cytopenia (neutropenia or autoimmune thrombocytopenia); malignancy (lymphoma); family history of affected limb. Such criteria need to be associated with: a marked decrease in IgG levels (assessed at least twice); normal or increased IgM levels (assessed at least twice); absence of secondary causes of hypogammaglobulinemia; no evidence of profound T cell deficiency (TCD4 defined as 2/3 of the reference values); absence of T cell proliferation; no evidence of ataxia-telangiectasia (coffee brown spots, ataxia, telangiectasia, increased alpha-fetoprotein levels).[30]

Patients with CD40 or CD40L disorders, due to the defective interaction between T and B, are more susceptible to infections that depend on IgA, IgG and IgE, with repetitive episodes of sinusitis, otitis, tonsillitis, cutaneous infections, giardiasis, helminthiasis, enterovirus meningitis, pneumonia, in addition to impairment of weight and height gain, and a tendency to autoimmune diseases and neoplasms. As in most cases, serum IgM is normal or increased, and the patient generally responds well to infections caused by Gram-negative bacteria. In addition to the resulting T-B interaction, patients with CD40L deficiency may consequently present with neutropenia, with a tendency to infections caused by *Staphylococcus aureus* and *Aspergillus fumigatus*. There may be specific disorders of TCD8 cells, such as an increased susceptibility to opportunistic infections by *Pneumocystis jirovecci*, *Toxoplasma gondii*, *Cryptosporidium spp*. and *Cryptococcus spp*. There is an even greater tendency for the development of autoimmune diseases and neoplasms. There may be chronic diarrhea and liver disease.[11,31–33]

Some presentations of CD40L deficiency progress with milder phenotypes, late onset of signs and symptoms, few complications, and a rapid response to treatment.[14,15,21,34] Mild phenotypes are associated with hypomorphic mutations that do not completely alter the expression and function of the CD40L protein, which makes diagnosis more difficult.[21,34–36] Patients with mild phenotypes of CD40L deficiency are often initially diagnosed with variable common immunodeficiency (CIVD), characterized by IgG and IgA deficiency, which may or may not include IgM deficiency, after other causes of hypogammaglobulinemia have been ruled out. These patients usually present with late clinical manifestations, normal IgM dosages and decreased IgG, IgA and IgE levels, which calls for genetic tests before a correct diagnosis can be reached.[20,34,37]

Complementary tests and differential diagnoses

Complementary laboratory tests for diagnosing CD40L deficiency initially include determining serum immunoglobulin levels and showing decreased serum IgG, IgA and IgE, with either normal or increased IgM levels. The in vitro analysis of lymphocyte function shows impaired T-cell proliferation, as well as an intrinsic defect in B-cell differentiation.[1,2]

Other Inborn Errors of Immunity should also be included when differentially diagnosing class-switch recombination defects, which requires complementary tests: quantification of CD19 or CD20 (away from BtK deficiency or Bruton's syndrome), assessment of CD3 and CD16/56 (away from severe combined immunodeficiency).[38,39] In order to confirm the diagnosis, it is necessary to analyze the expression of soluble CD40 and CD40L (CD154) proteins, which can be done by flow cytometry. In CD40L deficiency, memory B lymphocytes (CD27) may be decreased. Genetic studies contribute to confirming the diagnosis of CD40L deficiency and to the differential diagnosis with CD40 and CIVD deficiency, and may show a 6-nucleotide insertion mutation in the CD40L exon-1, confirming the diagnosis of CD40L deficiency and ruling out CIVD.[34]

Treatment

Treatment for class-switch recombination defects depends on the type of deficiency involved. Treatment for CD40 deficiency is antibiotic prophylaxis or human immunoglobulin replacement therapy, in addition to an early diagnosis of infections, so that antibiotics or antifungals can be administered whenever needed.[5,38,40]

The cure treatment for CD40L deficiency is the transplantation of hematopoietic stem cell transplantation, such as bone marrow transplantation, after a risk-benefit approach has been considered in each case, with such a procedure being usually reserved for severe cases and infections that are difficult to control. In the absence of transplantation, the treatment involves human immunoglobulin replacement, in addition to early treatment of infections.[36,40–45]

There are also efficacy and safety studies on treating CD40L deficiency with recombinant CD40L cells (rCD40L).[31,46,47] Umbilical cord blood-derived mesenchymal cell transplantation has been studied, but there is no consolidated data yet.[44]

In cases of severe and persistent neutropenia, therapy with granulocyte growth-stimulating factor (G-CSF) may be required.[17,46,48] Trimethoprim/sulfamethoxazole prophylaxis may be required to avoid *P. jirovecii* infections and environmental precautions needs to be taken to reduce the risk of infection by *Cryptococcus neoformans*.[31,34] Some studies suggest a non-redundant role of the CD40L-CD40 interaction in neutrophil development and function, which could be improved in vitro by recombinant human IFN-γ, indicating a potential new therapeutic application for this cytokine.[49]

The follow-up of patients with CD40L deficiency should be continuous and geared to searching for autoimmune diseases or neoplasms. It is also necessary for the patient to constantly improve their personal hygiene and dietary habits, avoiding the intake of raw foods when they are not home-prepared, due to IgA deficiency.[46,47]

There is indication for antipneumococcal immunization in CD40L deficiency, although neutralizing antibodies in immunocompromised patients may decrease the response to vaccination in patients undergoing immunoglobulin replacement therapy. Such patients may benefit from immunization, since vaccine titers required to be considered protective vaccine are low. There are guidelines setting forth that the vaccine should be administered a few days prior to administering human immunoglobulin. Vaccines with attenuated pathogens are contraindicated in patients with severe CD40L deficiency and may be prescribed in mild and moderate deficiencies.[38,50,51]

CD40L deficiency is a nosological entity with special and often severe clinical manifestations, requiring specific treatment and follow-up, which makes it essential to differentiate between the other Inborn Errors of Metabolism, especially CD40 and CVD deficiency.

Conclusion

CD40L deficiency is currently classified as an inborn error of immunity affecting cellular and humoral immunity, manifesting itself as class-switch recombination defect. Immunodeficiencies having high or normal IgM levels while the other immunoglobulins are decreased may be cases of Inborn Errors of Metabolism affecting cellular and humoral immunity (CD40L and CD40 deficiency) or predominantly antibody (AID, UNG and NEMO deficiencies).

In CD40L deficiency, there is a decrease in serum IgG, IgA and IgE levels, but with normal or high IgM levels, as a consequence of a disorder in the cooperation between T and B lymphocytes. This prevents IgM from class-switching and leads to sinopulmonary and gastrointestinal conditions, infectious diseases, autoimmune diseases, neoplasms and impairment of weight and height gain. Neutropenia may also be present, with accompanying pyogenic bacterial infections. The function of T cells is defective, which in turn is responsible for predisposing the patient to opportunistic infections and neoplasms.

It is therefore necessary for CD40L deficiency to be considered when differentially diagnosing Inborn Errors of Immunity, especially CD40 and CIVD deficiencies, whenever the patient presents with low serum IgG, IgA and IgE levels in combination with either normal or high serum IgM levels. The differential diagnosis between CD40L and CD40 deficiencies requires that soluble CD40 and CD40L proteins be determined. The genetic study contributes to the diagnosis. Severe cases of CD40L deficiency progress to cure when treated with hematopoietic stem cell transplantation. Milder cases and CD40 deficiency usually respond to prophylactic antibiotic therapy or to human immunoglobulin replacement therapy.

The differential diagnosis of CD40L deficiency among other Inborn Errors of Immunity is important, especially when one considers the specific treatment for patients with severe conditions, since therapy allows the condition to progress to cure, which in turn prevents sequelae and a poor progression.

Declarations of interest

None.

Authors contributions

Luiz Fernando Bacarini Leite and Tiago Arruda Máximo — the conception and design of the study, or acquisition of data, or analysis and interpretation of data, and drafting the article or revising it critically for important intellectual content.

Wilma Carvalho Neves Forte and Tainá Mosca — drafting the article or revising it critically for important intellectual content, and final approval of the version to be submitted.

References

1. Bousfiha A, Jeddane L, Picard C, Ailal F, Bobby Gaspar H, Al-Herz W, et al. The 2017 IUIS phenotypic classification for primary immunodeficiencies. J Clin Immunol. 2018;38:129–43.
2. Etzioni A, Ochs HD. The hyper IgM syndrome — an evolving story. Pediatr Res. 2004;56:519–25.
3. Rawat A, Mathew B, Pandiarajan V, Jindal A, Sharma M, Suri D, et al. Clinical and molecular features of X-linked hyper IgM syndrome — an experience from North India. Clin Immunol. 2018;195:59–66.
4. Rosen FS, Kevy SV, Merler E, Janeway CA, Gitlin D. Recurrent bacterial infections and dysgamma-globulinemia: deficiency of 7S gamma-globulins in the presence of elevated 19S gamma-globulins. Report of two cases. Pediatrics. 1961;28:182–95.
5. Burtin P. An example of atypical agammaglobulinemia (a case of severe hypogammaglobulinemia with increase of the beta-2 macroglobulin). Rev Fr Etud Clin Biol. 1961;6:286–9.
6. Klaver SG, Condino-Neto A. Defeitos genético-moleculares e aspectos clínicos de pacientes com síndrome de Hiper IgM autossômica. In: Dissertação de mestrado) Instituto de Ciências Biológicas da USP. 2011. p. 111.
7. Kavanaugh AF, Huston DP. Variable expression of IgG2 deficiency. J Allergy Clin Immunol. 1990;86:4–10.
8. Notarangelo LD, Lanzi G, Peron S, Durandy A. Defects of class-switch recombination. J Allergy Clin Immunol. 2006;117:855–64.
9. Winkelstein JA, Marino MC, Ochs H, Fuleihan R, Scholl P, Geha R, et al. The X-linked hyper-IgM syndrome. Clinical and immunologic features of 79 patients. Medicine. 2003;82:373–84.
10. Lougaris V, Badolato R, Ferrari S, Plebani A. Hyper immunoglobulin M syndrome due to CD40 deficiency: clinical, molecular, and immunological features. Immunol Rev. 2005;203:48–66.
11. Revy P, Mutto T, Levy Y, Geissmann F, Plebani A, Sanal O, et al. Activation-induced cytidine deaminase (AID) deficiency causes the autosomal recessive form of the Hyper-IgM syndrome (HIGM2). Cell. 2000;102:565–75.
12. Meyers G, Ng YS, Bannock JM, Lavoie A, Walter JE, Notarangelo JD, et al. Activation-induced cytidine deaminase (AID) is required for B-cell tolerance in humans. Proc Nat Acad Sci USA. 2011;108:11554–9.
13. Maul R, Gearhart P. AID and somatic hypermutation. Adv Immunol. 2010;105:159–91.
14. Wang LL, Zhou W, Zhao W, Tian Z, Wang WF, Wang XF, et al. Clinical features and genetic analysis of 20 Chinese patients with X-linked hyper-IgM syndrome. J Immunol Res. 2014;2014:683160, http://dx.doi.org/10.1155/2014/683160.
15. de la Morena MT. Clinical phenotypes of hyper-IgM syndromes. J Allergy Clin Immunol Pract. 2016;4:1023–36.
16. Lee W, Huang J, Yeh K, Yang M, Lai M, Chen L, et al. Clinical features and genetic analysis of Taiwanese patients with the hyper IgM syndrome phenotype. Pediatr Infect Dis J. 2013;32:1010–6.
17. Rezaei N, Aghamohammadi A, Ramyar A, Pan-Hammarstrom Q, Hammarstron L. Severe congenital neutropenia or hyper-IgM syndrome? A novel mutation of CD40 ligand in a patient with severe neutropenia. Int Arch Allergy Immunol. 2008;147:255–9.
18. Kracker S, Cardes P, Mazerolles F, Durandy A. Immunoglobulin class switch recombination deficiencies. Clin Immunol. 2010;135:193–203.
19. Stavnezer J. Molecular processes that regulate class switching. Curr Top Microbiol Immunol. 2000;245:127–68.
20. Grumach AS. Imunodeficiências predominantemente humorais. In: Grumach AS, editor. Alergia e imunologia na infância e na adolescência. 2 ed. São Paulo: Editora Atheneu; 2009. p. 533–55.
21. Buchbinder D, Park S, Nugent D. X-linked hyper IgM syndrome: a novel sequence variant associated with an atypical mild phenotype. J Pediat Hematol Onc. 2012;34:e212–4.

22. Xu Z, Zan H, Pone EJ, Mai T, Casali P. Immunoglobulin class-witch DNA recombination: induction, targeting and beyond. Nat Rev Immunol. 2012;12:517–31.
23. Kiani-Alikan S, Yong PF, Gilmour KC, Grosse-Kreul D, Davies EG, Ibrahim MA. Phenotypic heterogeneity in a family with a CD40 ligand intracellular domain mutation. J Clin Immunol. 2012;32:70–7.
24. Notarangelo LD, Peitsch MC. CD40lbase: a database of CD40L gene mutations causing X-linked hyper IgM syndrome. Immunol Today. 1996;17:511–6.
25. Ara A, Ahmed KA, Xiang J. Multiple effects of CD40-CD40L axis in immunity against infection and cancer. Immunotargets Ther. 2018;7:55–61.
26. Forte WCN. Imunoglobulinas. In: Forte WCN, editor. Imunologia do básico ao aplicado. 3 ed. São Paulo: Editora Atheneu; 2015. p. 51–65.
27. Chatzigeorgiou A, Lyberi M, Chatzilymperis G, Nezos A, Kamper E. CD40/CD40L signaling and its implication in health and disease. Biofactors. 2009;35:474–83.
28. Okuno Y, Hoshino A, Muramatsu H, Kawashima N, Wang X, Yoshida K, et al. Late-onset combined immunodeficiency with novel IL2RG mutation and probable revertant somatic mosaicism. J Clin Immunol. 2015;35:610–4.
29. Cabral-Marques O, Ramos RN, Schimke LF, Khan TA, Amaral EP, Bonfim CCB, et al. Human CD40 ligand deficiency dysregulates the macrophage transcriptome causing functional defects that are improved by exogenous IFN-γ. J Allergy Clin Immunol. 2017;139:900–12.
30. BRAGID. Brazilian Group for Immunodeficiencies. Acessado em 8/setembro/2018. In: http://www.imunopediatria.org.br.
31. Jain A, Kovacs JA, Nelson DL, Migueles SA, Pittaluga S, Fanslow W, et al. Partial immune reconstitution of X-linked hyper IgM syndrome with recombinant CD40 ligand. Blood. 2011;118:3811–7.
33. Kutukculer N, Moratto D, Aydinok Y, Lougaris V, Aksoylar S, Plebani A, et al. Disseminated cryptosporidium infection in an infant with hyper-IgM syndrome caused by CD40 deficiency. J Pediatr. 2003;142:194–6.
34. França TT, Leite LFB, Maximo TA, Lambert CG, Zurro NB, Forte WCN, et al. A novel de novo mutation in the CD40 ligand gene in a patient with a mild X-Linked hyper-IgM phenotype initially diagnosed as CIVD: New aspects of old diseases. Front Pediatr. 2018;6:1–8.
35. Elgueta R, Benson MJ, de Vries VC, Wasiuk A, Guo Y, Noelle R. Molecular mechanism and function of CD40/CD40L engagement in the immune system. Immunol Rev. 2009;229:152–72.
36. Cabral-Marques O, Klaver S, Schimke LF, Ascendino EH, Khan TA, Pereira PV, et al. First report of the Hyper-IgM syndrome registry of the Latin America Society for Immunodeficiencies: Novel mutations, unique infections and outcomes. J Clin Immunol. 2014;34:146–56.
37. Kokron CM, Barros MT. Imunodeficiências primárias. In: Kalil J, Motta A, Agondi R, editors. Alergia e Imunologia clínica: aplicação clínica. São Paulo: Editora Atheneu; 2015. p. 294–325.
38. Goudouris ES, Silva AMR, Ouricuri AL, Grumach AS, Condino-Neto A, Costa-Carvalho BT, et al. II Consenso Brasileiro sobre o uso de imunoglobulina humana em pacientes com imunodeficiências primárias. Rev Einstein. 2017;15:1–16.
39. Kanegae MPP, dos Santos AMN, Cavalcanti CM, Condino-Neto A. Triagem neonatal para imunodeficiência combinada grave. Rev Bras Alerg Imunopatol. 2011;34:7–11.
40. Bayrakci B, Ersoy F, Sanal O, Kilic S, Metin A, Tezcan I. The efficacy of immunoglobulin replacement therapy in the long-term follow-up of the B-cell deficiencies (XLA, HIM, CVID). Turk J Ped. 2005;47:239–46.
41. Tomizawa D, Imai K, Ito S, Kajiwara M, Minegishi Y, Nagasawa M, et al. Allogeneic hematopoietic stem cell transplantation for seven children With X-linked hyper-IgM syndrome: a single center experience. Am J Hematol. 2004;76:33–9.
42. Tseng M, Ge S, Roberts R, Kuo C, Choi J, Nissen NN, et al. Liver transplantation in a patient with CD40 ligand deficiency and hyper-IgM syndrome: clinical and immunological assessments. Am J Transplant. 2016;16:1626–32.
43. Lobo FM, Scholl PR, Fuleihan RL. CD40 ligand-deficient t cells from X-linked hyper-IgM syndrome carriers have intrinsic priming capability. J Immunol. 2002;168:1473–8.
44. Ziegner UH, Ochs HD, Schanen C, Feig SA, Seyama K, Futatani T, et al. Unrelated umbilical cord stem cell transplantation for X-linked immunodeficiencies. J Pediatr. 2001;138:570–3.
45. Gennery AR, Slatter MA, Grandin L, Taupin P, Cant AJ, Veys P, et al. Transplantation of hematopoietic stem cells and long-term survival for primary immunodeficiencies in Europe: entering a new century, do we do better? J Allergy Clin Immunol. 2010;126:602–10.
46. Leven EA, Maffuci P, Ochs HD, Scholl PR, Buckley RH, Fuleihan RL, et al. Hyper IgM syndrome: A report from the USIDNET regist. J Clin Immunol. 2016;36:490–501.
47. Hoeyveld EV, Zhang PX, Boeck KD, Fuleihan R, Bossuyt X. Hyper-immunoglobulin M syndrome caused by a mutation in the promotor for CD40L. Blackwell Publishing Ltd. Immunology. 2007;120:497–501.
48. Santos LFM, Mukai AO, Bertoli CJ, Fernandes TA, Suetugo CP, Santos LFM, et al. Relato de um caso de neutropenia congênita grave em um lactente jovem. Rev Paul Pediatr. 2011;29:680–4.
49. Cabral-Marques O, França TT, Al-Sbiei A, Schimke LF, Khan TA, Feriotti C, et al. CD40 ligand deficiency causes functional defects of peripheral neutrophils that are improved by exogenous IFN-γ. J Allergy Clin Immunol. 2018;142:1571–88.
50. Shearer WT, Fleisher TA, Buckley RH, Ballas Z, Ballow M, Blaese MR, et al. Recommendations for live viral and bacterial vaccines in immunodeficient patients and their close contacts. J Allergy Clin Immunol. 2014;133:961–6.
51. Bonilla FA. Update: vaccines in primary immunodeficiency. J Allergy Clin Immunol. 2018;141:474–81.