Review article

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WHAT IS BENTA DISEASE?

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Abstract

BENTA disease represents a newly defined entity in immunology. It is a primary immunodeficiency (PID) characterized by B Cell Expansion with NF-κB and T Cell Anergy (BENTA). This rare genetic disorder is transmitted in an autosomal-dominant manner and classified as a predominantly antibody deficiency by International Union of Immunological Societies (IUIS). The cause of the disease is a gain-of-function mutation in the CARMA1 (CARD11) gene. Clinically, the disease is manifested at an early age with hepatosplenomegaly, lymphadenopathy, anemia, susceptibility to frequent respiratory tract infections, and a low response to certain vaccines. Lymphadenopathies can be part of the clinical spectrum of several PIDs and can pose a significant diagnostic dilemma. Patients with this disease, carry a risk of developing chronic B-cell leukemia. Thorough family history is an important element in the assumption of diagnosis of BENTA disease. Treatment options of BENTA disease are still being considered, and can include splenectomy, application of monoclonal antibodies such as rituximab to deplete B cell reserve, wearing special „spleen guards“ when playing sports, and antibiotics for infections. Because it can present a burden for families, psychological support and counseling may be necessary. Each physician should be

informed about existence of this disease, so they could eventually recognize it in their medical practice.

Key words: BENTA, lymphadenopathy, CARMA1, PID.

Pregledni rad

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ŠTA JE BENTA BOLEST?

Sažetak

BENTA bolest predstavlja novodefinisani entitet u imunologiji. Pripada primarnim imunodeficijencijama (PID) i karakteriše je B-ćelijska ekspanzija sa NF-kB i T-ćelijskom anergijom (BENTA). Ovaj retki genetski poremećaj prenosi se autozomno-dominantnim putem i klasifikovan je od strane Internacionalnog udruženja imunoloških društava (IUIS) u predominantne deficijencije antitela. Uzrok ove bolesti je "gain-of-function" mutacija u CARMA1 (CARD11) genu. Klinički se ova bolest prezentuje u ranom dobu sa hepatosplenomegalijom, limfadenopatijom, anemijom i skonošću ka čestim respiratornim infekcijama, kao i smanjenom odgovoru na određene vakcine. Limfadenopatija može biti deo kliničkog spektra ispoljavanja nekolicine PID-a i može predstavljati dijagnostičku dilemu. Pacijenti sa ovom bolešću nose rizik za razvoj hronične B-ćelijske leukemije. Temeljna porodična anamneza bitni je element u postavljanju sumnje na BENTA bolest. Terapijske opcije u BENTA bolesti su još uvek u razmatranju i uključuju splenektomiju, primenu monoklonskih antitela poput rituksimaba kako bi smanjili broj B-limfocita, nošenje specijalnih štitova za slezinu pri bavljenju sportovima, kao i antibiotike za lečenje infekcija. Zbog toga što može predstavljati teret za čitavu prodicu, psihološko savetovanje može biti neophodno. Smatramo da svaki lekar treba biti upoznat sa postojanjem ove bolesti kako bi je eventualno mogao prepoznati u svojoj praksi.

Ključne reči: BENTA, limfadenopatija, CARMA1, PID.

Introduction

Primary immunodeficiency diseases (PID) are a group of hereditary and genetic disorders characterized by immune system dysfunction, leading to increased susceptibility to infections, autoimmunity, organ damage, and eventual malignancy (**Error! Reference source not found.**). Caspase recruitment domain-containing membrane-associated guanylate kinase protein-1 (CARMA1, also known as CARD11) is a protein in a CARD-CC protein family, important for T cell and B cell function, and activated after B cell receptor or T cell receptor stimulation. CARMA1 consists of 1) N-terminal CARD domain, 2) central coiled-coil (CC) domain, 3) C-terminal region containing a PDZ homology domain, 4) SH3 domain, and 5) guanylate kinase (GUK) domain (1, 3). There have been reported several heterozygous missence gain of function mutations (GOF) of this gene (C49Y, G123S, G123D, E134G, K215del, H234Ldel235-8). Dysfunction of this gene, which is extremely sensitive to mutations and genetic variation (4), could lead to atopic disease, immunodeficiency, and cancer (5-7). Activation of CARMA1 subsequently leads to activation of transcription factor NF-κB, an important factor for lymphocyte activation, survival, and proliferation (8, 9). Dysregulation of NF-κB could lead to autoimmunity, septic shock, and cancer (**Error! Reference source not found.**), and increased NF-κB activity is found in oropharyngeal, prostate, and pancreatic cancer. This kind of dysfunction protects cells from apoptosis and promotes cell mitosis and angiogenesis (10). Increased access to the Next generation sequencing (NGS) has contributed to the discovery of the genetic footprint of many primary immunodeficiencies and their subsequent classification. B cell expansion with NF-κB and T cell anergy (BENTA disease, see Figure 1) is a newly revised and classified as a predominantly antibody deficiency by the International Union of Immunological Societies

(IUIS) (1,13). BENTA disease is an extremely rare genetic, autosomal-dominant disorder (Figure 2) caused by gain-of-function mutation in the CARMA1 gene important in T cell and B cell function (14). The disease is characterized by polyclonal B lymphocyte expansion, splenomegaly and lymphadenopathy at an early age, mild immunodeficiency, and an increased risk for the development of lymphoma. Because of extreme rarity and complexity, there are no established guidelines or protocols for the treatment of this disease.

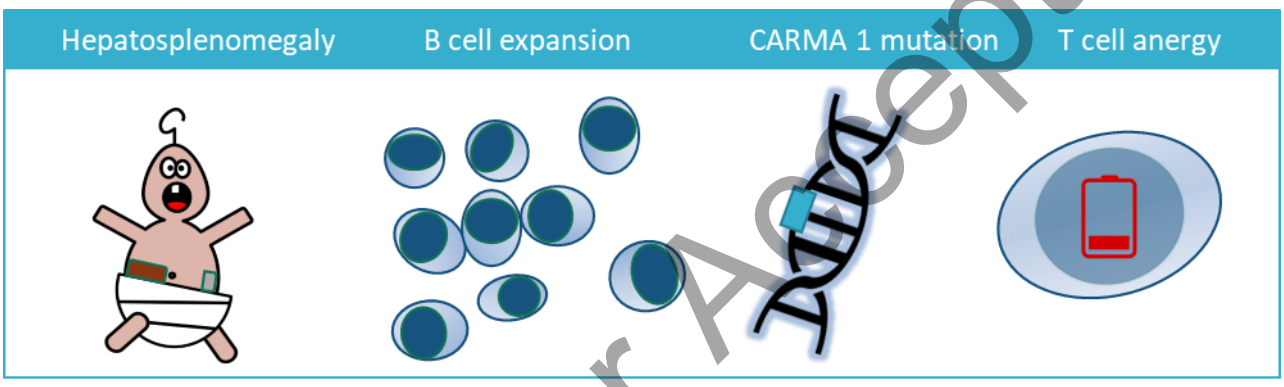

Figure 1. BENTA disease features.

BENTA disease is caused by a CARMA-1 gene mutation and is characterized by early-onset hepatosplenomegaly and B-cell expansion with T-cell anergy.

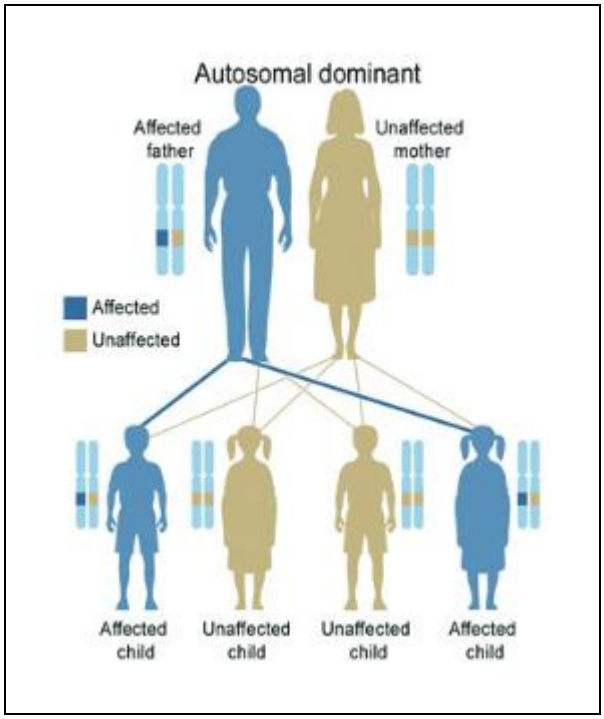

Figure 2. Autosomal-dominant nature of inheritance of BENTA disease.

BENTA disease is characterized by an autosomal-dominant inheritance. With one affected (heterozygous) parent, each child has a 50% chance of being affected.

Materials and methods

A thorough search of the literature and the MEDLINE database was made. Search terms: CARD11, BENTA disease, primary immunodeficiency, NF-kB.

Discussion

Immunological aspects

B cells play an important role in adaptive immunity. They are activated in secondary lymphoid organs (spleen, lymph nodes) and are involved in the pathogenesis of many autoimmune, malignant, and infective diseases (15, 16). BENTA patients show an increased production of B

cells in bone marrow. Immunologic phenotyping may show that ~50-80% of peripheral blood mononuclear cells are $CD19^{+}CD20^{+}CD5^{int}$ polyclonal naïve mature B cells (above normal range) representing mainly polyclonal, IgD^{hi} naïve mature B cells, with a significant elevation of $CD10^{+}CD24^{hi}CD38^{hi}$ transitional B cells (12). This is because B cell differentiation to plasma cells is impaired in patients with BENTA, even with additional in vitro cytokine stimulation (17). Therefore, patients could have an extremely low number of class-switched B cells, as well as a low number of memory B cells. Circulating B cells in these patients are also more prone to apoptosis, and their increased number is not a consequence of increased turnover or survival, as Snow et al (18) mentioned. NK cells are important in antiviral immunity and the removal of tumor cells. They are part of the innate immune system, and their function is analogous to cytotoxic T cells of adaptive immunity. NK cells are important in the pathogenesis of autoimmune diseases and can be used therapeutically in the treatment of malignancies (19, 20). BENTA patients could have decreased NK cells activity which was shown in vitro for G126D mutation on immortalized HeLa cell line. This mutation also leads to an independent antigen receptor signaling immune response (21). Several patients showed low serum levels of IgM antibodies, with IgA and IgG antibodies in the lower end of the normal range, whereas a total number of T cells fell within the normal range (22). CARMA1 aggregates can be detected, and quantification may show marginally elevated levels. In these patients there is also a weak response to polysaccharide-conjugate vaccines, while some patients also showed weak response to varicella and measles vaccine (23, 24). The spleen may be enlarged, resembling the splenic architecture of an older individual (24), or it may show characteristics of splenic marginal zone lymphoma, which include expansion of white pulp follicles and significant infiltration of red pulp with minimal cytological atypia and occasional binuclear lymphocytes (25). Individuals with a C49Y mutation in the CARMA1 (CARD11)

gene, located outside the LATCH-CC region, exhibit a milder form of adult BENTA disease. Predisposition to mild respiratory infections and low Candida albicans antigen-specific proliferation was noted in three patients with this mutation (26). As already mentioned, CARMA1 mutation causes NF-κB overactivity despite a lack of stimulation by T cell and B cell receptors that are usually triggered by a pathogen (18). Inadequate activation of NF-κB leads to activation of genes involved in the survival of transitional and naïve B lymphocytes and, paradoxically, to a weaker T cell responsivity to IL-2, which causes T cell anergy in the states of inflammation (27). Although NF-κB is involved in the pathogenesis of BENTA disease, the downstream signaling itself is preserved with CD40 stimulation and plasmablast differentiation after CD40 and IL-21 stimulation in vitro. The said cannot explain severe antibody deficiency, and some other mechanism of T and B cell interaction may play a role in vivo antibody deficiency (12). Elevated double negative T cell count could present a potential problem in differential diagnosis. Namely, T cell elevation with lymphadenopathy is also encountered in Autoimmune lymphoproliferative syndrome (ALPS), but absolute T cell count remains in normal range in BENTA patients and show weak response to in vitro stimulation with impaired IL-2 secretion and proliferation (12, 23, 28). The main early distinction between the two remains the CARMA1 genetic mutation which is detected only in BENTA patients.

Clinical aspects

Clinically, the disease begins to manifest itself with lymphadenopathy and hepatosplenomegaly in infancy. The cause of this manifestation of BENTA disease is in lymphocyte tendency to sequestrate in these organs (29, 30). Lymphadenopathies can be part of the clinical spectrum of several PIDs and can pose a significant diagnostic dilemma (31). Some rare diseases that manifest with lymphadenopathy at an early age are shown in figure 3.

Hemophagocytic lymphohistiocytosis (HLH) can also be included in differential diagnosis. HLH is characterized with some overlapping features such as lymphadenopathy, splenomegaly, and hepatomegaly (32). As in ALPS, some patients can be prone to certain autoimmune phenomena such as autoimmune hemolytic anemia, immune thrombocytopenia, hives (28). Mild immunodeficiency could predispose these patients to episodes of recurrent sinusitis, pneumonias, and in some cases towards infection to certain pathogens such as Epstein–Barr virus (EBV), Molluscum contagiosum virus (MCV), and BK virus (18, 33). Nonspecific symptoms such as fatigue, night sweats, loss of body mass with loss of appetite, could suggest a development of complication of BENTA towards B cell lymphocytic leukemia (34). Thorough family history is an important element in the assumption of diagnosis of BENTA disease. Others are of course, laboratory findings with eventual genetic testing, which provides definitive diagnosis. The autosomal-dominant nature of inheritance means that the offspring will have a 50% chance for getting the disease (Figure 2). Splenectomy could potentially cause complications due to lymphocytosis and increased risk for infection with encapsulated pathogens because splenic macrophages play an important role in protection against these bacteria (35, 36). It can also increase risk for B cell malignancy (28). In some cases, low number of NK cells (caused by CARMA1 mutation) could predispose BENTA patients to persistent Epstein-Barr virus (EBV) viremia (37-39). Following splenectomy, the number of NK cells and T cells could increase, which can point to an important role of splenic tissue as a niche for these cells (33). Because of weak response to certain vaccines, potential splenectomy could increase the risk of infection without possibility of protecting these individuals with usual immunization against Haemophilus influenzae, Streptococcus pneumoniae etc. (40, 41). Clinical manifestations of BENTA disease may depend on

additional genetic mutations, interaction with environmental factors and exposure to infections (26).

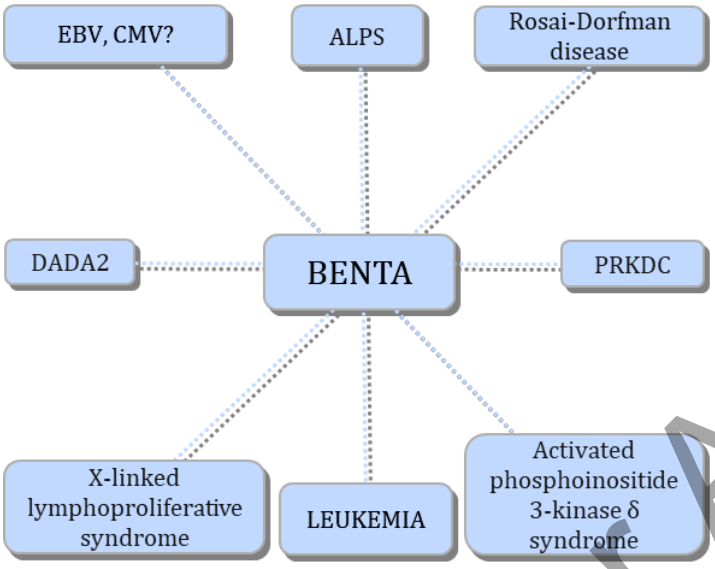

Figure 3. Example of disorders with lymphadenopathy in infancy

Many rare diseases present with lymphadenopathy in infancy, and congenital infections with CMV, EBV, and others are another possible cause of lymphadenopathy. Autoimmune lymphoproliferative syndrome (ALPS) is caused by lymphocyte apoptosis/homeostasis dysregulation. Rosai-Dorfman disease is characterized by the presence of excess histocytes in lymph nodes. Deficiency of Adenosine Deaminase 2 is an autosomal recessive disorder characterized by systemic inflammation, cytopenia, immunodeficiency, and early onset stroke. PRKDC mutation causes defects in the DNA repair mechanism and impairs the V(D)J recombination process. This is known to be one of the rare causes of Severe combined immunodeficiency (SCID). X-linked lymphoproliferative syndrome (XLA) is characterized by immunodeficiency and a predisposition to hemophagocytic lymphohistiocytosis. It predominantly affects males. Leukemia in infancy is a rare cause of lymphadenopathy at an

early age. Activated PI3K-delta syndrome is characterized by lymphadenopathy but low circulating T and B lymphocytes.

Treatment options

Treatment options of BENTA disease are still being considered. One possible role is given to monoclonal antibodies such as rituximab which could deplete B cell reserve. This approach is already used in treatment of autoimmune diseases (12, 42). Methotrexate can also be used to reduce and control lymphocytosis after splenectomy (23). Sirolimus (Rapamycin), an mTOR inhibitor is used in ALPS patients and can be used in BENTA patients as well in order to reduce lymphocyte burden (28. 43). In every case, a regular follow up is a necessity. MALT1 protease is a paracaspase involved in activation of NF-κB and therefore in the production of IL-2 and development of T cells and B cells. MALT1 protease inhibitors may have a potential role in management of BENTA disease (44, 45). Transfusions of blood and blood products may be needed if anemia and thrombocytopenia occur (46). Splenomegaly is a potential risk for spleen rupture and patients with BENTA are sometimes required to wear “spleen guards” when playing sports. Counselling may be beneficial because of potential high psychological stress encountered by individuals with BENTA disease and their families. Families may also benefit from meeting or talking to other families affected by the same rare disease. Hematopoietic stem cell transplantation could be curative and is effectively used in other immunodeficiency states (47). In case of disease complication with development of leukemia, treatment would involve chemotherapy with stem cell transplantation (48). There are still no studies to prove the eventual benefit of prophylactic antibiotic use in PID patients, although

this kind of practise is common (49, 50). Antiviral treatment of EBV and Chronic active Epstein-Barr virus (CAEBV) infection is generally ineffective. Immunomodulatory treatment (IFN-α, IFN-γ) had also shown small success in CAEBV (51, 52). In this case, allogenic hematopoietic stem cell transplant could be applied, as it is used for certain indications in PID (53).

Conclusion

BENTA disease is a novel, not yet fully understood, but significant immunological entity. The nature of the disease is such, so it can pass unnoticed because of broad array of clinical manifestation and its rarity. Small number of reported cases in the literature can be a consequence of the clinicians not recognizing the disease. We think that each physician should be informed about existence of this disease, so they could eventually recognize it in their medical practice.

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