**Review article**

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# WHAT IS BENTA DISEASE?

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B cell expansion with NF-κB and T cell anergy (BENTA) represents a newly defined entity in immunology. It is a primary immunodeficiency (PID). This rare genetic disorder is transmitted in an autosomal dominant manner and classified as a predominantly antibody deficiency by the International Union of Immunological Societies (IUIS). The cause of the disease is a gain-of-function mutation in the Caspase recruitment domain-containing membrane-associated guanylate kinase protein-1 (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. They 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 the existence of this disease so they can eventually recognize it in their medical practice.

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***Key words:*** *B cell expansion with NF-κB and T cell anergy, lymphadenopathy, Caspase recruitment domain-containing membrane-associated guanylate kinase protein-1, primary immunodeficiency diseases*

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## 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 (1). Caspase recruitment domain-containing membrane-associated guanylate kinase protein-1 (CARMA1), also known as CARD11, is a member of the CARD-CC protein family and plays a critical role in T and B cell function. CARMA1 is activated following stimulation of the B cell receptor (BCR) or T cell receptor (TCR). CARMA1 is organized into several distinct domains, including an N-terminal CARD domain, a central coiled-coil (CC) domain, a PDZ homology domain, an SH3 domain, and a C-terminal guanylate kinase (GUK) domain (1, 2). Several heterozygous missense gain-of-function (GOF) mutations in this gene have been reported, including C49Y, G123S, G123D, E134G, K215del, and H234Ldel235–238. Dysfunction of this gene, which is highly sensitive to mutations and genetic variation (3), can lead to atopic disease, immunodeficiency, and cancer (4–6). Activation of CARMA1 subsequently leads to activation of transcription factor NF-κB, an important factor for lymphocyte activation, survival, and proliferation (7, 8). Dysregulation of NF-κB could lead to autoimmunity, septic shock, and cancer (9), 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 (9). 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 newly revised and classified as a predominantly antibody deficiency by the International Union of Immunological Societies (IUIS) (1). 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 (10). 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 (4). Due to its extreme rarity and complexity, there are no established guidelines or standardized protocols for the treatment of this disease.

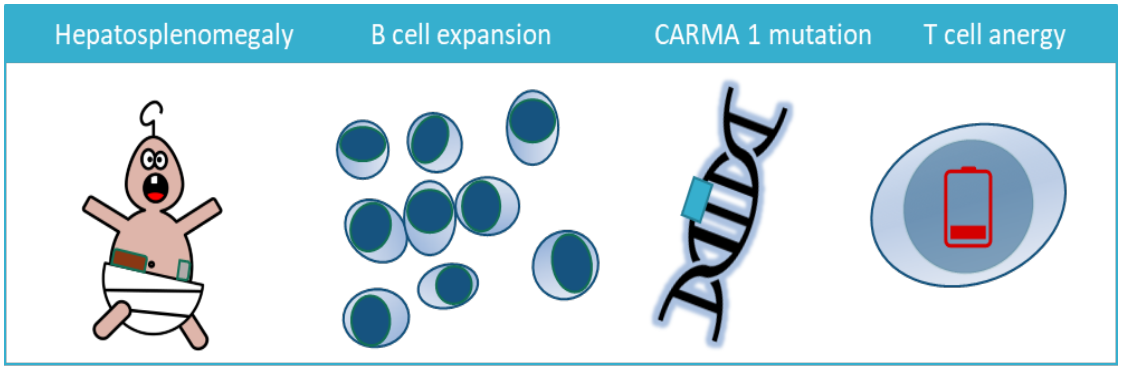


**Figure 1.** BENTA disease features

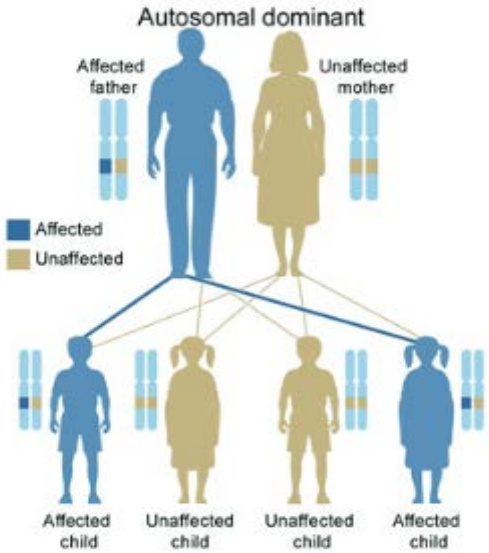


**Figure 2.** Autosomal dominant nature of inheritance of BENTA disease

## Materials and Methods

A thorough search of the literature and the MEDLINE database was conducted using the following search terms: CARD11, BENTA disease, primary immunodeficiency, and NF-κB.

## 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 (11, 12). BENTA patients show an increased production of B cells in bone marrow. Immunological 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 (13). This is because B cell differentiation to plasma cells is impaired in patients with BENTA, even with additional in vitro cytokine stimulation (14). 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. mentioned (15). 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 (16, 17). BENTA patients may exhibit decreased natural killer (NK) cell activity, as demonstrated in vitro for the G126D mutation using immortalized HeLa cell lines (16, 17). This mutation also induces antigen receptor–independent immune activation (18). Several patients have been reported to show low serum levels of IgM antibodies, with IgA and IgG levels at the lower end of the normal range, while the total number of T cells generally remains within normal limits (19). CARMA1 aggregates can be detected, and their quantification may reveal marginally elevated levels. Affected individuals often exhibit a weak immune response to polysaccharide-conjugate vaccines; some also display diminished responses to varicella and measles vaccines (20, 21). The spleen may be enlarged, resembling the splenic architecture of an older individual (21), or it may show characteristics of splenic marginal zone lymphoma, which include the expansion of white pulp follicles and significant infiltration of red pulp with minimal cytological atypia and occasional binuclear lymphocytes (22). 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 were noted in three patients with this mutation (23). As 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 (24). 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 (13). 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 the normal range in BENTA patients and shows weak response to *in vitro* stimulation with impaired IL-2 secretion and proliferation. The main early distinction between the two remains the CARMA1 genetic mutation, which is detected only in BENTA patients (13, 20, 25).

## 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 (26, 27). Lymphadenopathies can be part of the clinical spectrum of several PIDs and can pose a significant diagnostic dilemma (28). 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 by some overlapping features such as lymphadenopathy, splenomegaly, and hepatomegaly (29). As in ALPS, some patients can be prone to certain autoimmune phenomena such as autoimmune hemolytic anemia, immune thrombocytopenia, and hives (25). 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 (15, 30). Nonspecific symptoms such as fatigue, night sweats, and loss of body mass with loss of appetite could suggest a development of complication of BENTA towards B cell lymphocytic leukemia (31). A thorough family history is a crucial component in the initial suspicion of BENTA disease. Laboratory findings, supplemented by genetic testing, are essential for establishing a definitive diagnosis. The autosomal dominant nature of inheritance means that the offspring will have a 50% chance of 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 (32, 33). It can also increase the risk for B cell malignancy (25). In some cases, a low number of NK cells (caused by CARMA1 mutation) could predispose BENTA patients to persistent Epstein–Barr virus (EBV) viremia (34–36). 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 (30). Because of weak response to certain vaccines, a potential splenectomy could increase the risk of infection without the possibility of protecting these individuals with usual immunization against *Haemophilus influenzae, Streptococcus pneumonia,* etc. (37, 38). Clinical manifestations of BENTA disease may depend on additional genetic mutations, interaction with environmental factors and exposure to infections (23).

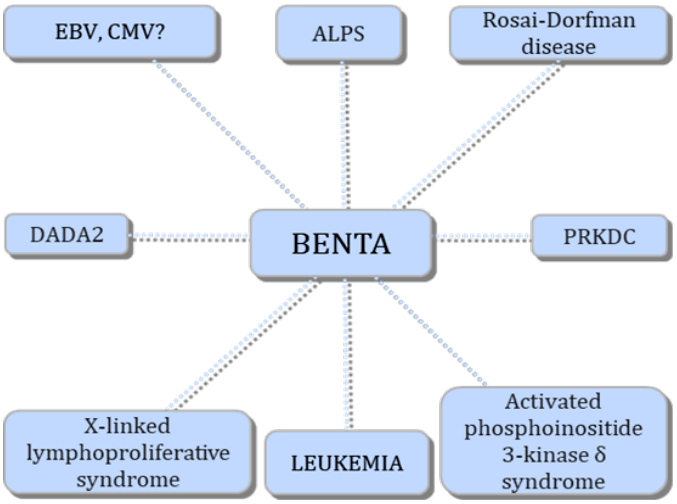


**Figure 3**. Example of disorders with lymphadenopathy in infancy

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 (1, 39).

## Treatment options

Treatment options for BENTA disease are still under investigation. One possible role is given to monoclonal antibodies such as rituximab, which could deplete B cell reserve. This approach is already used in the treatment of autoimmune diseases (13, 40). Methotrexate can also be used to reduce and control lymphocytosis after splenectomy (20). Sirolimus (Rapamycin), an mTOR inhibitor, is used in ALPS patients and can be used in BENTA patients as well to reduce lymphocyte burden (25, 39). In all patients, a regular follow-up is a essential. MALT1 protease is a paracaspase involved in the activation of NF-κB and, therefore, in the production of IL-2 and the development of T cells and B cells. MALT1 protease inhibitors may have a potential role in the management of BENTA disease (41, 42). Transfusions of blood and blood products may be needed if anemia and thrombocytopenia occur (43). 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 (44). In case of disease complications with the development of leukemia, treatment would involve chemotherapy with stem ce ll transplantation (31). There are still no studies to prove the eventual benefit of prophylactic antibiotic use in PID patients, although this kind of practice is common (45, 46). Antiviral treatment of EBV and Chronic active Epstein–Barr virus (CAEBV) infection is generally ineffective. Immunomodulatory treatment (IFN-α, IFN-γ) has also shown small success in CAEBV (47, 48). In such cases, allogeneic hematopoietic stem cell transplantation (HSCT) may be considered, as it is an established therapeutic option for certain forms of PID (49).

## Conclusion

BENTA disease is a recently characterized, incompletely understood, but clinically significant immunological disorder. Its wide spectrum of clinical manifestations, combined with its rarity, contributes to frequent underrecognition. The limited number of reported cases likely reflects a lack of awareness among clinicians rather than true incidence. Enhancing physician familiarity with BENTA disease is essential to improve early recognition, diagnosis, and appropriate management in clinical practice.

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# ŠTA JE BENTA BOLEST?

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BENTA (engl. B-cell expansion with NF-jB and T-cell anergy – BENTA) bolest predstavlja pojavu koja je nedavno definisana u imunologiji. BENTA bolest spada u primarne imunodeficijencije (engl. *primary immunodeficiency* – PID). Karakteriše je B-ćelijska ekspanzija sa NF-kB i T-ćelijskom anergijom. Ovaj retki genetski poremećaj prenosi se autozomno dominantnim putem. Internacionalno udruženje imunoloških društava (engl. *International Union of Immunological Societies* – IUIS) svrstalo ga je u predominantne deficijencije antitela. Uzrok ove bolesti jeste *gain-of-function* mutacija u CARMA1 (engl. *Caspase recruitment domain-containing membrane-associated guanylate kinase protein-1* – CARMA1) (CARD11) genu. Ova bolest klinički se prezentuje u ranom dobu hepatosplenomegalijom, limfadenopatijom, anemijom i skonošću ka čestim respiratornim infekcijama, kao i smanjenim odgovorom na određene vakcine. Limfadenopatija može biti deo kliničkog spektra ispoljavanja nekolicine PID-a i može predstavljati dijagnostičku dilemu. Kod osoba sa ovom bolešću postoji rizik od razvoja hronične B-ćelijske leukemije. Temeljna porodična anamneza predstavlja važan element kada postoji sumnja na BENTA bolest. Kao načini lečenja BENTA bolesti, koji se i dalje ispituju, navode se splenektomija, primena monoklonskih antitela poput rituksimaba radi smanjenja broja B-limfocita, nošenje specijalnih štitova za slezinu prilikom bavljenja sportom, kao i antibiotici za lečenje infekcija. Budući da oboleli mogu predstavljati teret za čitavu porodicu, psihološko savetovanje može biti neophodno. Verujemo da svaki lekar treba biti svestan postojanja ove bolesti kako bi je mogao prepoznati u svojoj praksi.

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***Ključne reči**: B-cell expansion with NF-jB and T-cell anergy, limfadenopatija, Caspase recruitment domain-containing membrane-associated guanylate kinase protein-1, primarna imunodeficijencija*