ACTA SCIENTIFIC MICROBIOLOGY (ISSN: 2581-3226)

Volume 2 Issue 1 January 2019

Research Article

Report Cases: Selective IgM Deficiency: An Underestimated Primary Immunodeficiency and Vitamin D Associated Beta-Glucana Injectable in Impact on Immune Functions: Implications for Preventive Strategy of Infection Disease

Fabrício Prado Monteiro*

Allergy and Immunology West Bahia, Barreiras, Bahia, Brazil

***Corresponding Author:** Fabrício Prado Monteiro, Allergy and Immunology West Bahia, Barreiras, Bahia, Brazil.

Received: November 21, 2018; **Published:** December 20, 2018

Abstract

IgM is the first immunoglobulin to be expressed on the surface of B cells and the first immunoglobulin isotype secreted during an initial immune response to an exogenous antigen. Mature naïve B cells in response to antigens undergo clonal expansion and differentiation into Ig-secreting cells. A subset of activated IgM+ B cells undergo a process of heavy chain isotype switching resulting in the production of antibodies of different isotypes such as IgG, IgA, and IgE, upon engagement of CD40 with CD40L and interaction with cytokines, and somatic hyper mutation in V region results in the selection of high affinity antibody producing B cells [1,2].

In contrast to secreted IgG, IgM comes in two ways, pre-immune or without exposure to exogenous antigen also known as "natural IgM" that is spontaneously produced, and the second type is exogenous antigen-induced or "immune" IgM antibodies. In addition to providing early defence against microbes, natural IgM plays an important role in immune homeostasis, and provide protection from consequences of infections and inflammation [1,3].

Beyond its well-known effects on calcium homeostasis and bone mineralization, vit. D has become recognized as a pluripotent immunoregulator of biological functions with a particular role in immune tolerance and antimicrobial immunity. The expression of the vit. D receptor (VDR) in many immune cells have led to recognition of the associations between the vit. D metabolism and infections, allergic and cronic auto immune disorders [4-6].

Immunostimulating subcutaneous therapy as proposed, according to protocol and subcutaneous and muscular administration bimonthly of glucan and glucoronidase (ITA BG®) associated with VIT.D 600.000 UI (HERVA'S PINEDA PHARMACIAS®), providing an increase of antigenic recognition because of an efficient activation of antigen presenting cells through up-regulation of their receivers [7,8].

Thus, the activation and degranulation of inflammatory products that because various clinical manifestations are minimized and regulated, with the consequent clinical improvement and no adverse effects.

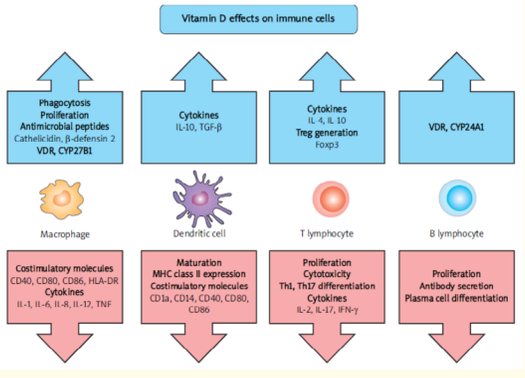

Figure 1

Keywords: Vitamin D; Infection; Disease

Introduction

SIGMD has been reported in a number of chromosomal abnormalities, including chromosome 1,18 and 22q11.2 [9,10]. The most common association of SIGMD has been with 22q11.2 deletion syndrome [9,11-13].

The features clinical are similar to other primary immunodeficiency disorders, patients with SIGMD commonly present with recurrent infections with common microbes, and increased frequency of allergic and autoimmune diseases.

Recurrent infections as the presenting manifestation occur in more than 80% of patients with SIGMD. Some of these bacterial infections may result in serious life-threatening infections [10,14-16]. The clinical infectious presentations of SIGMD include recurrent otitis media, chronic sinusitis, bronchitis, bronchiectasis, pneumonia, urinary tract infections, cellulitis, meningitis, sepsis, etc. Some of the most common microbial organisms include *Streptococcus pneumoniae, Hemophilus influenzae, Neisseria meningitidis, Pseudomonas aeruginosa, Aspergillus fumigatus, Giardia lamblia*; many of these organisms' express epitopes of phosphorylcholine in their cell walls that are similar to those expressed on apoptotic cells and recognized by natural IgM.

In children with SIGMD, allergic and autoimmune diseases are infrequent [17], whereas in adults, allergic and autoimmune diseases are frequently present [18,19].

Almost 40% of patients with SIGMD display allergic manifestations. Several investigators have reported association between atopic diseases and SIGMD [18-21]. The frequency of asthma and allergic rhinitis in SIGMD in reported cases ranged from 30 to 45%.

Beyond its well-known effects on calcium homeostasis and bone mineralization, vitamin D has become recently recognized as a pluripotent immunoregulator of biological functions with a particular role in immune tolerance and antimicrobial immunity. Although extensive research has been carried out on the vitamin D action, its molecular and cellular mechanisms have not been fully elucidated thus far.

Humans obtain vitamin D in two different forms as prohormones, namely as cholecalciferol or vitamin D3, a product of the photochemical reaction in keratinocytes from 7 dehydrocholesterol by exposure to sunlight as well as ergosterol or vitamin D2, synthesized in plants exposed to UVB radiation. The former mechanism provides 80% of vitamin D to the human organism, although both cholecalciferol and ergosterol may also be obtained from animal and plant dietary products, respectively [22].

The proximal kidney tubule is admittedly the primary place of the latter process, however many cell types, including monocytes/macrophages, dendritic cells and lung epithelial cells are capable of synthesizing 1,25(OH)2D3 [23,24].

These data in conjunction with expression of the vitamin D receptor (VDR) in many immune cells have led to the recognition of the associations between the vitamin D metabolism and chronic autoimmune, infectious, allergic, cardiovascular, neoplastic, and neurodegenerative disorders [25,26].

We evaluated 15 patients from the Institute of Allergy and Immunology Dr. Fabrício Prado Monteiro (IMUNOPED) from August 2013 to August 2017 with clinical and laboratory diagnosis of IGM Deficiency (clinical manifestations and basic pathologies associated with IgM levels lower than the 3rd percentile based on the Brazilian population and vitamin D deficiency, with levels lower than 30 ng/dl) (MARIA FUJIMURA and NAGAO DIAS APPEARANCE - NORMALITY VALUES OF IMMUNOGLOBULINS (A, G and M) AND IGG SUB-CLASSES (MG/DL).

In this period, we performed the protocol of injectable doses of immunostimulant ultra-low bimonthly doses (ITA BG - 9 doses/patient) associated with injectable and bi-monthly dose of Vit. D 600,000 IU (PINEDA) (6 doses/patient) with the primary objectives (Clinical improvement and remission of associated baseline disease) and secondary (IGM levels above the 25th percentile and vit. D levels between 60-90 ng/dl) were achieved relatively and absolutely.

Patients and Methods

Fifteen patients were selected after inclusion and exclusion criteria (below).

These were submitted to bimonthly and injectable treatment of VITAMIN D 600,000 IU PINEDA and IMMUNOSTIMULATION WITH EPD - BETAGLUCANA AND BETAGLUCORONIDASE (ITA BG), from August 2013 to August 2017.

The patients in question received a total of nine doses of ITA BG and six doses of vitamin D.

The inclusion criteria were as follows:

- Serum IgM below p3 for reference (less than 81 mg/dl) (MARIA FUJIMURA and NAGAO DIAS APPEARANCE - NORMALITY VALUES OF IMMUNOGLOBULINS (A, G and M) AND IGG SUB-CLASSES (MG/DL)
- And serum levels of vitamin D below 30 ng/dl.

The exclusion criteria were as follows:

- No use of immunosuppressive medications or systemic corticosteroids.

The baseline clinical diagnoses associated with hypovitaminosis D and selective IgM deficiency were as follows:

- Allergic Rhinitis (five),
- Asthma (three),
- Atopic Dermatitis (three),
- Allergic Contact Dermatitis (three),
- Urticaria Vasculitis (one),
- Splenectomy Accidental (one),
- Migraine (one),
- Chronic Fatigue (one).

Total doses ITA BG IMUNOCENTER used: 135 doses (total time of use: one year and eight months).

Total doses VIT.D 600,000 IU HERVA'S/PINEDA PHARMACIAS used: 90 doses (total time of use per patient: twelve months).

There were no local adverse effects in the applications and idem without systemic alterations (fever and infections - secondary to the applications) observed in the determined period (both zero occurrences).

In all patients, we reached the pre-determined primary and secondary goals described below:

- **Main objective:** Clinical improvement of signs and symptoms and use of emergency medications for basic diseases;
- **Secondary goals:** serum vit. D between 60-90 ng/dL and serum IgM levels above p25 for the reference given (above 103 mg/dl).

Results

We evaluate the results obtained through the measures of central tendency and we believe with this to be more assertive.

Adjusting therapeutic medical conduct with the consequent reduction of additional costs to the patient and return of the quality of life and substantial improvement of its underlying disease and related complications and comorbidities.

Fashion

Fashion is called the most frequent of a set.

Median

If the information set is numeric and is organized in ascending or descending order, its median is the number that occupies the center position of the list.

Mean (M)

More precisely called simple arithmetic mean, is the sum of all the information in a data set divided by the number of information that has been summed.

The mean is the most used centrality measure because it is the one that most uniformly blends the lowest and highest values in a list.

The weighted average (Mp) is an extension of the simple mean and considers weights for the data set information.

It is done by summing the product of an information by its respective weight and then dividing that result by the sum of all the weights used.

Despite the established inclusion criteria, the following common characteristics were diagnosed in one hundred percent (100%) of the patients: atopic patients with selective serum IgM deficiency and serum vitamin D deficiency (IgE increased, IgM below the 3rd percentile for corresponding age and vitamin D levels below 30 ng/dL.

As a basic diagnosis observed by medical practice (anamnesis and physical examination) we had the following diagnoses of associated comorbidities: five (5) patients with Allergic Rhinitis; three (3) Asthma patients; two (2) patients with Atopic Dermatitis; two

(2) patients with Allergic Contact Dermatitis); one (1) patient with Urticaria/Vasculitis and; one (1) patient with Migraine.

The mode of diagnosis was Allergic Rhinitis, a common upper respiratory inflammatory syndrome that causes personal, financial disorders and causes loss of quality of life and incapacitating co-morbidities to the patients in question.

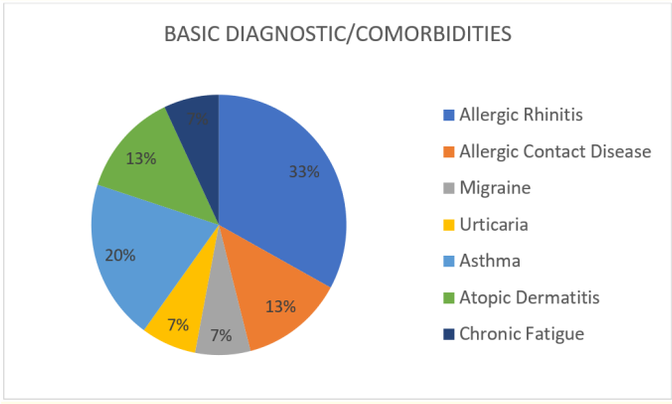

Figure 2

In relation to gender, we obtained a discrete prevalence of females (8 females/7 males).

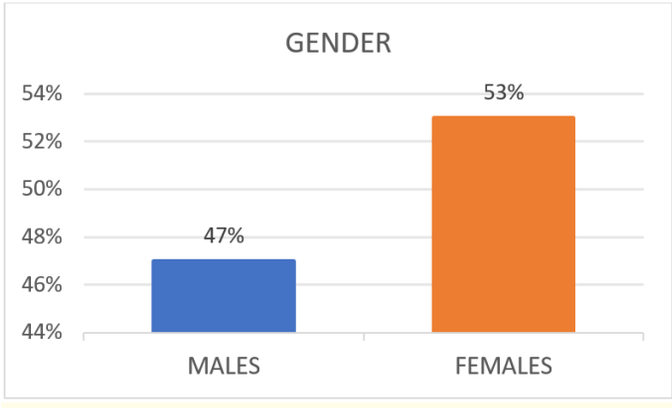

Figure 3

Twelve patients (12) were in the adult age range (12 years to 60-65 years), two (2) patients in the children range (zero to 12 years old) with 4 and 5 years of age respectively and one patient in the elderly age group (over 60-65 years old) with ninety-four (94yo) years of age.

In relation to trend measures there was a weighted average of thirty-six (36y.o) years of age. The minimum age is four years (4yo) of age and the maximum of ninety-four (94y.o) years of age.

The median was thirty-five years (35yo) and with a bimodal prevalence, 30 years and 35 years.

These epidemiological data are very important, since they reinforce the importance of preventive and cost-effective medical measures in relation to the complications, hospitalizations and purchases of therapeutic medications (antibiotics and anti-inflammatories) necessary for acute diseases and crises.

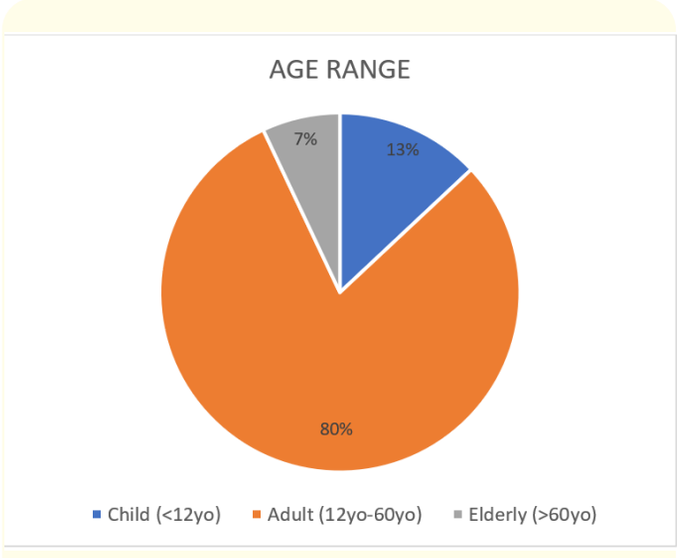

Figure 4

We determined the measures of tendency to objectively assess the clinical improvement of the patients relative to the reduction of the number of hospitalizations (during the study period we had only two occurrences, one due to asthma and one due to migraine); the reduction of the use of antibiotics in the period of eighteen (18) months was a maximum of 3 times a year, including steroidal and nonsteroidal anti-inflammatory drugs.

Trend measures remove biological biases and are commonly used to define medical trends and behaviors, reducing unnecessary costs to patients, public and private institutions.

In all patients we were able to reach the primary goals highlighted above (reduction of hospitalizations, reduction of antibiotics and anti-inflammatories and reduction of hospitalization and me-

dical emergencies) and secondary objectives (increase in serum IgM levels above the 25th percentile of the reference used and increased serum vitamin D levels between 60-90 ng/dl).

Importantly, the fifteen patients studied had their serum IgM levels above the 50th percentile (above 123 mg/dl).

In reference to the bi-monthly subcutaneous dosage of ITA BG (IMUNOCENTER LTDA), we obtained the following data: median of seven (7) doses; fashion of eight (8) doses; and a mean of six (6) doses, to obtain the pre-determined results.

All patients performed 9 doses of ITA BG IMUNOCENTER in the period of 18 months.

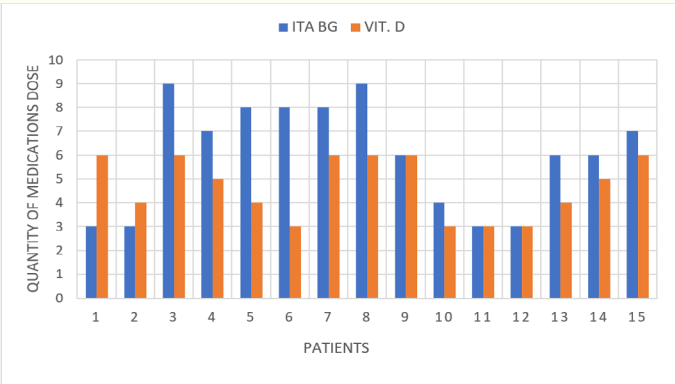

Figure 5

In reference to the intramuscular performance of VITAMIN D 600,000 IU HERVA'S PINEDA PHARMACIES LTDA, we obtained the following data: median of four (4) doses; fashion of six (6) doses and; average of four (4) doses, to obtain the pre-determined results.

All patients performed 6 doses of VITAMIN D 600,000 IU in the 12-month period.

Discussion

In this medical article we had a primary objective (clinical improvement of the underlying disease and decrease of comorbidities) and secondary (serum levels of vitamin D and serum immunoglobulin M adjusted) achieved, as were all medical articles performed and based on a validated scientific line throughout medical history.

However, we also seek to focus the Pharmacoeconomics on the patient jointly the quality of life that the patient can obtain mainly observing prevention (secondary, tertiary and quaternary) so that we stimulate more and more such a successful medical practice.

The vitamin D effects on the immune phenomena have been translated into implications regarding the relationship between the vitamin D status and the risk of allergic diseases.

The impact of 1,25(OH)2D3 on the fetal lung growth and development as well as surfactant production in alveolar type II cells [27], in conjunction with the effect on the developing immune system and promotion of the protolerogenic phenotype leads to questions about the role of vitamin D in the development of asthma.

Several studies showed a positive correlation between either the maternal serum 25(OH)D3 during pregnancy or the higher vitamin D intake as well as the reduced risk of respiratory tract infections and early childhood wheezing in the offspring [27,28], the effect that might be owing both to the immunoregulatory activity of vitamin D and also to its antiviral actions [29].

Furthermore, in a study by Miyake., *et al*. [30] the protective effect of maternal diary food and vitamin D intake during pregnancy was not exclusively confined to respiratory symptoms, but the reduced risk of eczema in infants was also demonstrated.

Another group of clinical studies was aimed at the assessment of the relationship between vitamin D status and allergic disease severity. The first epidemiological study demonstrating an association between low vitamin D levels and increased markers of asthma severity, including serum IgE, eosinophil count, the use of inhaled corticosteroids and hospitalization rate in the previous year was conducted among school children in Costa Rica [31].

Subsequently, higher odds of severe asthma exacerbations were shown by the same group of researchers in the Childhood Asthma Management Program Study in North American children [32].

The role of vitamin D as a possible preventive measure for asthma was explored in the study by Majak., *et al* [33].

The authors demonstrated that vitamin D supplementation during a period from September to July prevented decline of serum 25(OH) D3, the effect that was associated with a reduced risk of asthma exacerbations triggered by acute respiratory tract infections.

In our study we agreed with all articles reported and our sample was selected with 100 percent of atopic patients, that is, predisposed to allergic diseases due to genetic and hereditary condition of excess production of allergy antibodies (IgE) to external stimuli antigens).

Similar to other primary immunodeficiency disorders, patients with SIGMD commonly present with recurrent infections with common microbes, and increased frequency of allergic and autoimmune diseases. These clinically features have been reviewed in detail [34].

Recurrent infections as the presenting manifestation occur in more than 80% of patients with SIGMD. In children with SIGMD, allergic and autoimmune diseases are infrequent [17], whereas in adults, allergic and autoimmune diseases are frequently present [18,19].

Almost 40% of patients with SIGMD display allergic manifestations. Several investigators have reported association between atopic diseases and SIGMD [18-21]. The frequency of asthma and allergic rhinitis in SIGMD in reported cases ranged from 30 to 45%.

The precise mechanism of IgM-mediated regulation of tolerance is unclear, a number of mechanisms have been proposed: (a) cross-linking of FcμR and BCR by IgM autoantibodies-self-antigen complexes resulting in the induction of anergy or deletion of B cells; (b) loss of central tolerance as a result of BCR editing at the level bone marrow; (c) loss of peripheral tolerance secondary to a deficiency of isotype-specific regulatory lymphocytes; (d) impaired clearance of apoptotic cells/bodies (self-antigens).

In SIGMD patients, we did not observe any significant changes in the expression of FcμR on any of B cell subsets except low-level expression on MZ B cells [35].

Therefore, it is unlikely that changes in FcμR or peripheral tolerance play a significant role in the development of autoimmunity in SIGMD. Patients with SIGMD also have decreased proportions of CXCR3+ B cells [36]. Recently, a deficiency of CXCR3+ B cells has been linked to autoimmune diseases [37].

Our clinical and laboratory observations allowed clinical and immunological homeostasis of the patients studied while serum vitamin D levels were between 30 and 60 ng/dl and serum and non-specific serum IgM levels were higher than p25 and more precisely above p50 for used reference. (MARIA FUJIMURA and NAGAO DIAS APPEARANCE – NORMALITYVALUES OF IMMUNOGLOBULINS (A, G and M) AND IGG SUB-CLASSES (MG/DL).

Thus, we believe, as proposed, in the action of immunological homeostasis through the regulation of immunoglobulin M. In contrast to secreted IgG, IgM comes in two ways, pre-immune or without exposure to exogenous antigen also known as “natural IgM” that is spontaneously produced, and the second type is exogenous antigen-induced or “immune” IgM antibodies.

The majority of circulating IgM is comprised of natural IgM antibodies. It has been established from studies of mutant mice deficient in IgM secretion that both natural and immune IgM are important in responses to pathogens and self-antigens [38,39].

The two prominent features of natural IgM are polyreactivity and autoreactivity, which are attributed to the germline configuration of their v region structures. The natural IgM antibodies are reactive with many conserved epitopes that are shared by microbes and self-antigens. The production of natural IgM appears to be triggered by interaction with self-antigens. In addition to providing early defense against microbes, natural IgM plays an important role in immune homeostasis, and provide protection from consequences of autoimmunity and inflammation [40,41].

It also appears that the specificity to bind to components of self-antigen is critical for protecting effect of natural IgM against autoimmunity. In mice, B1 cell-derived plasma cells are the major source of natural IgM, and natural IgM promotes the T cell-dependent antibody response by conventional B2 cells [42].

The immune IgM antibodies are selected for antigen-specificity that are usually produced in response to pathogens and serve as a first line of defense against microbial infections and also provide protection from autoimmune diseases [38,40].

Conclusion

The use of beta-glucan and betaglucuronidase (ITA BG-IMUNOCENTER) in combination with vitamin D replacement (VIT.D HERVA'S PINEDA PHARMACIAS), both in an injectable form and with the modified protocol, allowed a clinical and laboratory rescue of the patients without increasing the cost and absence of adverse effects and necessity of hospitalization, when compared to the studies in which they show these patients needing venous replacement of human immunoglobulin, which are rich in IgM and idem, improves patients with cited above.

Given the potential for vitamin D to suppress inflammatory responses and enhance the antimicrobial pathway activity, it has been suggested that its deficiency might be blamed for the epidemic of allergic diseases.

The beta Glucuronidase is an agent stimulant of the immune system and has a desensitizing action under normal pH. This substance has an important role as immune response modifier that stimulates the expression of adhesion molecules by antigen-presenting cells in contact with lymphocytes and vice versa, in the intra-cellular space and acts on the balance shift TH2/TH1 [43,44].

Method with proven security, without cases of deaths to this date and large scale in Brazil since the early of the 90's was considered.

However, there are few available randomized double-blind studies.

Bibliography

1. Sudhir Gupta and Ankmalika Gupta. "Selective IgM Deficiency—An Underestimated Primary Immunodeficiency". *Front Immunology* 8 (2017): 1056.

2. Valdivieso JM and Fernandez E. "Vit. D receptor polymorphisms and diseases". *Clinica Chimica Acta* 371 (2006): 1-12.

3. Goutham Dronavalli., *et al*. "Selective IgM deficiency" (2008).

4. Holick MF. "Vit. D deficiency". *New England Journal* 357 (2007): 266-281.

5. Holick MF. "Vitamin D status: measurement, interpretation, and clinical application". *Annual Epidemiology 1*9 (2009): 73-78.

6. Hewison M. "Vit D and the immune system: new perspectives on an old theme". *Endocrinology and Metabolism Clinics of North America* 39 (2010): 365-379

7. Monteiro FP. "Recurrent Vulvo-Vaginites and Immune System (RVVC)". *Journal of Clinical Case Reports* 3.3 (2018).

8. "Fabrício Prado Monteiro". *Journal of Allergy and Therapy* 8:3 (2017):

9. Al-Herz W., *et al*. "22q11.2 deletion syndrome and selective IgM deficiency: an association of a common chromosome abnormalities with a rare immunodeficiency". *American Journal of Medical Genetics* 127 (2004): 99-100.

10. Hong R and Gupta S. "Selective IgM deficiency in an adult with Streptococcus pneumoniea sepsis and invasive aspergillosis". *Journal of Investigational Allergology and Clinical Immunology* 18.3 (2008): 214-218.

11. Shubert MS and Moss RB. "Selective polysaccharide antibody deficiency in familial DiGeorge syndrome". *Annals of Allergy* 69 (1992): 231-238.

12. Haddad ZH., *et al*. "IgA, IgM and partial deletion of chromosome 18". *Lancet* 1 (1969): 92044-92043.

13. Kung S-J., *et al*. "Selective gM deficiency and 22q11.2 deletion syndrome". *Annals of Allergy, Asthma and Immunology* 99 (2007): 87-92.

14. Hobbs JR., *et al*. "Gamma-M deficiency predisposing to meningococcal septicaemia". *British Medical Journal* 4 (1967): 583-586.

15. Jones DM., *et al*. "Three cases of meningococcal infection in a family associated with a deficient immune response". *Archives of Disease in Childhood* 48 (1973): 742–743.

16. Zaka-ur-Rab Z and Gupta P. "Psuedomonas septicemia in selective IgM deficiency". *Indian Pediatrics* 42.9 (2005): 961-962.

17. Goldstein MF., *et al*. "Pediatric selective IgM deficiency". *Clinical and Developmental Immunology* (2008): 624850.

18. Goldstein MF., *et al*. "Selective IgM immunodeficiency: retrospective analysis of 36 adult patients with review of literature". *Annals of Allergy, Asthma and Immunology* 97.6 (2006): 717-7130.

19. Yel L., *et al*. "Clinical and immunological features in IgM deficiency". *International Archives of Allergy and Immunology* 150.3 (2009): 291-298.

20. Guill MF., *et al*. "IgM deficiency: clinical spectrum and immunological assessment". *Annals of Allergy* 62 (1989): 547-552.

21. Kaufman HS and Hobbs JR. "Immunoglobulin deficiencies in an atopic population". *Lancet* (1970): 1061-1063.

22. O'Mahony L., *et al*. "The potential role of vitamin D enhanced foods in improving vitamin D status". *Nutrients* 3 (2011): 1023-1041.

23. Hewison M. "Vitamin D and the intracrinology of innate immunity". *Molecular and Cellular Endocrinology* 321.2 (2010): 103-111.

24. Hansdottir S., *et al*. "Respiratory epithelial cells convert inactive vitamin D to its active form: potential effects on host defense". *The Journal of Immunology* 181.10 (2008): 7090-7099.

25. Holick MF. "Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardio - vascular disease". *The American Journal of Clinical Nutrition* 80.6 (2004): 1678S-88S.

26. Kulie T., *et al*. "Vitamin D: an evidence-based review". *American Board of Family Medicine* 22.6 (2009): 698-706.

27. Camargo CA Jr., *et al*. "Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at 3 y of age". *The American Journal of Clinical Nutrition* 85.3 (2007): 788-795.

28. Camargo CA Jr., *et al*. "Cord-blood 25- hydroxyvitamin D levels and risk of respiratory infection, wheezing, and asthma". *Pediatrics* 127.1 (2011): e180-e187.

29. Mansbach JM and Camargo CA Jr. "Respiratory viruses in bronchiolitis and their link to recurrent wheezing and asthma". *Clinics in Laboratory Medicine* 29 (2009): 741-55.

30. Miyake Y., *et al*. "Dairy food, calcium and vitamin D intake in pregnancy, and wheeze and eczema in infants". *European Respiratory Journal* 35.6 (2010): 1228-1234.

31. Brehm JM., *et al*. "Serum vitamin D levels and markers of severity of childhood asthma in Costa Rica". *American Journal of Respiratory and Critical Care Medicine* 179 (2009): 765-71.

32. Brehm JM., *et al*. "Serum vitamin D levels and severe asthma exacerbations in the Child - hood Asthma Management Program study". *Journal of Allergy and Clinical Immunology* 126 (2010): 52-58.

33. Majak P., *et al*. "Vitamin D supplementation in children May prezent astma exacerbation triggered by acute respiratory infection". *Journal of Allergy and Clinical Immunology* 127 (2011): 1294-1296.

34. Louis AG and Gupta S. "Selective IgM deficiency: an ignored primary immunodeficiency disease". *Clinical Reviews in Allergy and Immunology* 46 (2014): 104-111.

35. Gupta S., *et al*. "FcμR in human B cell subsets in primary selective IgM deficiency, and regulation of FcμR and production of natural IgM antibodies by IGIV". *Human Immunology* 77 (2016): 1194-2001.

36. Louis AG., *et al*. "Analysis of B cell subsets, Breg, CD4 Treg and CD8 Treg in adult patients with primary selective IgM deficiency". *American Journal of Clinical and Experimental Immunology* 5.1 (2016): 21-32.

37. Henneken M., *et al*. "Differential expression of chemokine receptors on peripheral blood B cells from patients with rheumatoid arthritis, and systemic lupus erythematosus". *Arthritis Research and Therapy* 7 (2005): R1001-R1013.

38. Boes M., *et al*. "Critical role of immunoglobulin M in immediate defense against systemic bacterial infection". *J Exp Med* 188.12 (1998): 2381-2386.

39. Nguyen TTT and Baumgarth N. "Natural IgM and development of B cell-mediated autoimmune diseases". *Critical Reviews in Immunology* 36 (2016): 163-177.

40. Boes M., *et al*. "Accelerated development of IgG autoantibodies and autoimmune diseases in absence of secreted IgM". *Proceedings of the National Academy of Sciences of the United States of America* 97.3 (2000): 1184-1189.

41. Ehrenstein MR and Notley CA. "The importance of natural IgM: scavenger, protector and regulator". *Nature Reviews Immunology* 10.11 (2010): 778-786.

42. Savage HP and Baumgarth N. "Characteristics of natural antibody secreting cells". *Annals of the New York Academy of Sciences* 1352 (2015): 132.

43. Monteiro FP. "Recurrent Vulvo-Vaginites and Immune System (RVVC)". *Journal of Clinical Case Reports* 3.3 (2018): 2573.

44. Fabrício Prado Monteiro". *Journal of Allergy and Therapy* 8 (2017): 3.

Volume 2 Issue 1 January 2019