Chapter 3

CONGENITAL DEFECTS OF PHAGOCYTES

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ABSTRACT

Congenital defects of phagocytes are primary immunodeficiency diseases (PIDs), a genetically heterogeneous group of disorders that affect distinct components of the innate immune system, such as neutrophils, macrophages, dendritic cells, and eventually others cells such as T and B lymphocytes and Natural Killer. These diseases involving myeloid differentiation, for example, in severe congenital neutropenia, Kostmann disease and neutropenia with cardiac and urogenital malformations. Congenital defects of phagocytes may also be associated with a range of organ dysfunction, for example, in Shwachman-Diamond syndrome (associated with pancreatic insufficiency), glycogen storage disease type Ib (associated with a glycogen storage syndrome), β-Actin deficiency (associated with mental retardation, short stature), pulmonary alveolar proteinosis (associated with alveolar proteinosis), and p14 deficiency (associated with partial albinism and growth failiure). Included in this group of congenital defects of phagocytes, leukocyte adhesion deficiency (LAD) is a disease characterized by defects in the leukocyte adhesion cascade. Currently, three types of LAD have been identified, LAD-1(deficiency of the integrin β2 subunit), LAD-II (absence of the ligand, SleX, affecting the leukocyte rolling) and LAD-III (caused by defects in G protein-coupled receptor-mediated integrin activation). Periodontal disease is most common in Rac 2 deficiency, Localized juvenile periodontitis and Papillon-Lefrève syndrome and to a lesser extended in Chronic Granulomatous Disease. Susceptibility to mycobacteria and *Salmonella* are common in defects of IL-12 and IL-23/IFN-γ axis and in minor proportion in hyper-IgE syndrome, whose patients are more likely to contract *Staphylococcus. In* general, treatment of phagocytes dysfunction should focus on prevention of infections, by use of antimicrobial prophylaxis, and recombinant granulocyte-colony-stimulating factor (G-CSF), usually tolerable, but if used at high doses, augments the spontaneous risk of leukemia in patients with congenital defects of phagocytes.

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Keywords: Phagocytic system; Neutrophils; Macrophages; Primary immunodeficiency; Congenital defects

Circulating monocytes and neutrophils are primary phagocytic cells in blood [1], which arise in the bone marrow from a common committed progenitor represented by granulocyte-macrophage colony-forming unit. After maturation, these cells differentiate in two distinct lineages, granulocytes and macrophages. The primary functions of these cells are engulfment and killing of microbes [2,3]. Adequate numbers of neutrophils and macrophages are necessary for normal host defense, and their functional activities include adherence to vascular endothelial cells, migration by diapedesis through capillary walls, recognition of microbes, phagocytosis, secretion of enzymes, and generation of oxygen toxic metabolite species involved in intracellular microbes killing [4,5]. Neutrophils are the most abundant leukocytes in blood, different from macrophages, present in lower numbers. Neutrophils live a short time in tissues, and die after host defense, different form macrophages [6]. In the tissues, macrophages assume immunoregulatory and phagocytic functions. Tissue macrophages include hepatic Kupffer cells, alveolar macrophage in lung, microglial cells in brain and dermal Langerhans cells.

Phagocytic cells are the first line of defense against microbes. Thus, genetic defects of number and function of phagocytes results in high susceptibility to infection of soft tissues, abscesses formation close to natural barriers and regional lymphadenitis [7,8,9,10]. Congenital phagocytes disorders affect primarily children [6,11,12]. Their classification is summarized in Table 1[13].

1. SEVERE CONGENITAL NEUTROPENIAS

Severe congenital neutropenias are a group of defects with autossomal dominant inheritance that affects myeloid differentiation and neutrophil production with prevalence of $3\text{-}4/1,0 \ \mathrm{x}10^6$ individuals [6,14]. Genetic defects were observed in *ELA2* (mistrafficking of elastase), *GFI1* (repression of elastase) and *G-CSFR* (receptor of G-CSF) [15,16,17]. Diagnostic criteria include neutropenia in early childhood (<500 cells/mm^3 blood), recurrent bacterial infections and disturbances in maturation of neutrophils in bone marrow [6,13,17]. Patients with severe congenital neutropenia present fever, severe and recurrent infections of the respiratory tract and skin during the first year of life [6]. Twenty percent of patients develop leukemia or myelodysplasia syndrome during adolescence [18]. One form of the disease is caused by mutation of *ELA2* gene, responsible for mistrafficking of elastase; *ELA2* is located on chromosome 19p13.31 and encodes protein neutrophil elastase 2, a serine protease present in azurophil or specific granules.

Table 1. Congenital defects of phagocyte number, function or both

Disease	Affected cells	Altered function	Associated features	Inheritance	Gene
Severe congenital neutropenias (3 forms)	N	Myeloid differentiation	Subgroup of patients with myelodysplasia (form 1)	AD	ELA2
			T/B lymphopenia (form 2)	AD	GFI1
			profound neutropenia (form 3)	AD	G-CSFR
Kostmann disease	N	Myeloid differentiation	Cognitive and neurological defects	AR	HAX1
Neutropenia with cardiac and urogenital malformations	N, F	Myeloid differentiation	Structural heart defects, urogenital abnormalities, and venous angiectasias of trunks and limbs	AR	G6PC3
Glycogen storage disease type 1b	N, M	Chemotaxis, O_2^- production, Killing	Fasting hypoglycemia, lactic acidosis, hyperlipidemia, hapatomegaly, neutropenia	AR	G6PT1
Cyclic neutropenia	N	?	Oscillations of neutrophils and platelets	AR	ELA2
X-linked neutropenia/myelodysplasia	N, M	?	Monocytopenia	X	WAS
p14 deficiency	N, L, Me	Endosome biogenesis	Neutropenia, hypogamaglobulinemia, lower TCD8 cytotoxicity, partial albinism, growth failure	AR	MAPBPIP
Leukocyte adhesion deficiency type 1	N, M, L, NK	Adherence, Chemotaxis, Endocytosis, T CD8/NK cytotoxicity	Delayed cord separation, skin ulcers, periodontitis, leukocytosis	AR	ITGB2
Leukocyte adhesion deficiency type 2	N, M	Rolling, Chemotaxis	Mild LAD type 1 features plush h-blood group plus mental and growth retardation	AR	FUCT1
Leukocyte adhesion deficiency type 3	N, M, L, NK	Adherence	LAD type 1 plus bleeding tendency	AR	KLINDLIN 3
Rac 2 deficiency	N	Adherence Chemotaxis, O_2^- production	Leukocytosis, poor wound healing	AD	RAC2
β-Actin deficiency	N, M	Motility	Mental retardation, short stature	AD	ACTB
Localized juvenile periodontitis	N	Formylpeptides-induced chemotaxis	Periodontitis only	AR	FPR1

Table 1. (Continued)

Disease	Affected cells	Altered function	Associated features	Inheritance	Gene
Papillon-Lefrève syndrome	N, M	Chemotaxis	Periodontitis, palmoplantar hyperkeratosis	AR	*CTSC*
Specific granules deficiency	N	Chemotaxis	Neutrophils with bilobed nuclei	AR	*CEBPE*
Shwachman-Diamond syndrome	N	Chemotaxis	Pancytopenia, exocrine pancreatic insufficiency, chondrodysplasia	AR	*SBDS*
X-Linked Chronic Granulomatous Disease (X-CGD)	N, M	0_2^- production, Killing	Recurrent life-tthreatening bacterial and fungal infection, granuloma formation, hepatosplenomegaly, McLeod phenotype in a subgroup of patients	X	*CYBB*
Autosomal CGD	N, M	0_2^- production, Killing	Same of X-CGD	AR	*CYBA, NCF1, NCF2, NCF4*
IL-12 and IL-23 receptor β1 chain deficiency	L, NK	IFN-γ secretion	Susceptibility to mycobacteria and *Salmonella*	AR	*IL12RB1*
IL-12p40 deficiency	M	IFN-γ secretion	Susceptibility to mycobacteria and *Salmonella*	AR	*IL12B*
IFN-γ receptor 1 deficiency	M, L	IFN-γ binding and signaling	Susceptibility to mycobacteria and *Salmonella*	AD, AR	*IFNGR1*
IFN-γ receptor 2 deficiency	M, L	IFN-γ signaling	Susceptibility to mycobacteria and *Salmonella*	AR	*IFNGR2*
STAT-1 deficiency (2 forms)	M, L	IFN-γ signaling (form 1) IFN-α, IFN-β, IFN-γ, IFN-λ,IL-27signaling (form 2)	Susceptibility to mycobacteria and *Salmonella* Susceptibility to mycobacteria, *Salmonella* and viruses	AR AD	*STAT1* *STAT1*
AD hyper-IgE syndrome	M, L, E	IL-6, IL-10, IL-12, IL-22,IL-23 signaling	Distinct facial features, eczema, osteoporosis and fractures, scoliosis, failure/delay of shedding primary teeth, hyperextensible joints, bacterial infections by *S. Aureus* and *C. albicans*	AD	*STAT3*

Disease	Affected cells	Altered function	Associated features	Inheritance	Gene
AR hyper-IgE syndrome (*TYK2* deficiency)	N, M, L	IL-6, IL-10, IL-12, IL-23, IFN-α, IFN-β signaling	Susceptibility to mycobacteria, *Staphylococcus*, *Salmonella* and viruses	AR	*TYK2*
AR hyper-IgE syndrome (*DOCK3* deficiency)	N, M, L	IL-6, IL-10, IL-12, IL-23, IFN-α, IFN-β signaling	Susceptibility to mycobacteria, *Staphylococcus*, *Salmonella* and viruses	AR	*DOCK3*
Pulmonary alveolar proteinosis	M	GM-CSF signaling	Alveolar proteinosis	Biallelic mutations in pseudoautosomal gene	*CSF2RA*

E=epithelial cells; F=Fibroblasts, L=Lymphocytes; M=Monocytes-macrophages; Me=Melanocytes; N=Neutrophils; NK=Natural Killer cells; AD=autosomal-dominant; AR=autosomal recessive; X= X-linked. font: *J Allergy Clin Immunol* 2009; 124: 1161-78. Erratum in: *J Allergy Clin Immunol* 2010; 125: 771-3.

Mutations in *ELA2* lead to premature apoptosis of myelocytes, interrupting normal cycle of maturation [14,15,16,18]. Another form of severe congenital neutropenia involves mutations in *GFI1* gene; a repressor of elastase, which affects myeloid differentiation [6,13]. This defect, in addition to agranulocytosis by maturation arrest of neutrophil precursors to promyelocytic stage, have T and B lymphopenia and hypogammaglobulinemia. Patients with *GFI1* mutation present with recurrent bacterial infections early in life, especially in the mouth and perineal region, and anemia and thrombocytopenia [6,14,15,16]. A third mutation form involves mutations in the *G-CSFR* gene responsible to the expression of G-CSF receptor in neutrophils [13], resulting in severe neutropenia and maturation arrest of marrow progenitor cells at the promyelocyte-myelocyte stage [6,14,15,16]. Treatment of patients with severe congenital neutropenias include, in moderate neutropenia complicated by superficial or profound infections, oral antibiotic therapy. Patients with severe neutropenia and sepsis require immediate hospitalization. Prophylactic antibiotics alone are insufficient, and before introduction of G-CSF, the projected median survival was only three years. Fortunately, over 90% of patients respond to pharmacological G-CSF with elevation in neutrophil counts and reduction in the number of infections and hospitalizations [19]. The best treatment of patients is the use of hematopoietic growth factors (G-CSF and GM-CSF) produced by genetic engineering. G-CSF is mostly used because GM-CSF has several disadvantages [20], with lower efficacy and poorer tolerability (flu-like syndrome and eosinophilia). Treatment increases the number of granulocytes, decreases the number of new infections and significantly improves survival and quality of life [21,22]. In severe and refractory cases, bone marrow transplant is the treatment of choice [23].

2. KOSTMANN DISEASE

Kostmann disease, severe congenital neutropenia, autossomal recessive type 3 or infantile genetic agranulocytosis are differents names of the same disease, an autossomal recessive inheritance caused by mutation in the *HAX1* gene, located on chromosome 12.13 [24,25]. This gene plays a significant role in apoptosis of neutrophils, preventing the differentiation of neutrophil to promyelocytes and myelocytes. The term, Kostmann disease is sometimes used inappropriately, for neutropenia with *ELANE* mutations. This disease is characterized by the early onset of serious infections and neutropenia (<200 cells/mm^3 blood), monocytosis, reactive eosinophilia, and strong susceptibility to bacterial infections [6,26]. The literature reports death of children under 3 years old. Bacterial infections commonly involve sinus, lungs, liver, skin and joints. Approximately 40% of patients have decreased bone density and osteoporosis. A small percentage of neurological and cognitive defects were associated with neutropenia [27]. Treatment of patients include management by multidisciplinary team, because external pancreatic insufficiency leads to nutritional deficiency; attention to bone disorders and abnormal mental development. The use of G-CSF is less frequent when compared with permanent *ELA2* neutropenia. In severe and refractory cases, bone marrow transplant is indicated [6].

3. NEUTROPENIA WITH CARDIAC AND UROGENITAL MALFORMATIONS

This disease is an autosomal recessive inheritance, caused by mutation in the *G6PC3* gene; with abolished enzymatic activity of glucose-6-phosphatase and enhanced apoptosis of neutrophils and fibroblasts [13,28]. Children with congenital neutropenia with cardiac and urogenital malformation have early onset recurrent bacterial infections and severe neutropenia (<200 cels/mm^3 blood), where 75% of affected children die before the age of 3. Patients with this disease present structural heart defects, urogenital abnormalities, and venous angiectasias of trunks and limbs. Treatment include G-CSF [29].

4. GLYCOGEN STORAGE DISEASE TYPE 1B

Glycogen storage disease type 1b has an autosomal recessive inheritance caused by mutation in *G6PT1* gene, responsible for the production of glucose-6-phosphatase transporter 1, important to transport glucose-6-phosphate into the lumen of the endoplasmatic reticulum. In the endoplasmatic reticulum, the G6Pase catalytic unit is located, responsible for the maintenance of blood glucose [6,30]. Patients present fasting hypoglycemia, hyperlipidemia, hepatoesplenomegaly, neutropenia, lactic acidosis with normal latent activity of glucose-6-phosphatase in liver [31,32,33]. Defects in motility, chemotaxis, oxidative burst and microbes killing, are attributed to poor microbial metabolism via anaerobic glycolysis and hexose monophosphate. Since neutrophils are responsible for the defense of mucocutaneous natural barriers [1,3,5], infections and ulceration of the oral/anal regions are common, including pneumonia and sepsis by *Staphylococcus aureus*, *Streptococcus* of group A and *Escherichia coli*. The use of G-CSF is indicated in severe cases of infections [34].

5. CYCLIC NEUTROPENIA

Cyclic neutropenia is an autosomal dominant disorder that affects the *ELA2* gene, responsible for mistrafficking of elastase, located on chromosome 10p13.3, which affects $1/1,0 \times 10^6$ individuals [6,13]. The major clinical manifestations include cyclic periods of neutropenia (<200 cells/mm^3 blood) and blood cell counts between zero and the lower limit of normal, lasting 3-10 days that occurs at intervals of 21 days, but can vary from 14-36 days. Neutropenia is accompanied by thrombocytopenia and monocytosis that occurs during neutropenia periods [35,36]. The most common symptoms during neutropenia are fever, malaise, periodontitis, oral mucosal ulceration, impetigo and lymphadenopathy [37]. Children and teenagers present oral mucosal ulceration, infection and lymphadenopathy during periods of neutropenia, while adults have mild to moderate neutropenia without well-defined cycles. Cellulitis and bacteremia are serious complications that can be fatal. The diagnosis includes blood tests twice a week during 6 weeks. The treatment consists of G-CSF use in symptomatic patients, increasing the time interval between neutropenia to values above 500 cells/mm^3 blood. Severe cases unresponsive to therapy require bone marrow transplantation [38,39].

6. X-LINKED NEUTROPENIA/MYELODYSPLASIA

X-linked neutropenia/myelodisplasia is rare form of congenital neutropenia, with X-linked inheritance, caused by the mutation in the *WAS* gene, a regulator of actin cytoesqueleton (loss of autoinhibition) of leukocytes [6,13]. Patients with this disease present severe recurrent infections during early life, neutropenia (<500 cells/m^3 blood)m and monocytopenia [40]. The disease is often diagnosed at an older age, because the infections are relatively mild. Since patients have dysplasia of bone marrow cells, they may develop leukemia [41]. Treatment involves the use of prophlylactic antibiotics. G-CSF use is recommended in cases of severe neutropenia with risk of sepsis in children because of the possible risk of leukemia development [6].

7. P14 DEFICIENCY

p14 deficiency is an autossomal recessive disorder characterized by neutropenia (<500 cells/mm^3 blood), hypogammaglobulinemia, low CD8 citotoxicity, partial albinism, and growth failure. The mutation is located in the *MAPBPIP* gene that encodes endosomal adaptor protein 14, located at lysosomes [13]. Absence of this protein causes structural and functional abnormalities of endosomes of CD8 T cells, neutrophils and melanocytes [42]. Patients present short stature, hypopigmentation of skin, recurrent bronchopulmonary infection by *Streptococcus pneumoniae* and pneumoniae. Clinical manifestations include oculocutaneous hypopigmentation and rough face appearance, dysfunction of CD8 T cells, low number of memory B cells (CD27$^+$IgM$^+$IgD$^+$), and hypogammaglobulinemia [6,13]. Diagnosis is confirmed by mutation in the *MAPBPIP* gene. Differential diagnosis include other causes of immunodeficiency with hypopigmentation like Chediak-Higashi Syndrome, Grisceli Syndrome type 2, Hermansky-Pudlak Syndrome, and hypoplasia of hair and cartilage [13]. Treatment of patients includes agressive therapy for acute bacterial infections and prophylactic antibiotics. Neutropenia is responsive to G-CSF therapy, and replacement of intravenous imunoglobulin (IVIG) is indicated in patients with hypogammaglobulinemia or specific antibody deficiency [6].

8. LEUKOCYTE ADHESION DEFICIENCY

Leukocyte adhesion deficiency (LAD) are a group of diseases classified in LAD-1, LAD-2, LAD-3, according to the immunological defect, associated features, and genetic defects [43]. Leukocyte adhesion deficiency type 1 (LAD-1), is an autosomal recessive disorder that affects $1/1 \times 10^6$ individuals, with mutations located in the *ITGB2* gene, that encodes the CD18 molecule that forms a heterodimer with CD11 (beta-2-integrin) expressed on the surface of neutrophils, macrophages, lymphocytes, and NK cells [13]. The main leukocyte-associated beta-2-integrins are leukocyte function-associated type 1 (LFA-1 or CD11a/CD18), Mac-1 or CR3 (CD11b/CD18), and p150, 95 or CR4 (CD11c/CD18) [1,2,4,44,45]. Patients with LAD-1 during acute infectious crises exhibit leukocytosis (>25.000 leukocytes/mm^3 blood) due too poor adhesion of neutrophils and macrophages to blood vessel walls, recurrent infections and

delayed umbilical cord separation, skin ulcers and periodontitis [6,13]. Affected sites include upper and lower airways; ulcerative lesions of the tongue, periodontitis and gingivitis. Main microbial agents include *Staphylococcus aureus, Excherichia coli, Pseudomonas aeruginosa, Proteus spp, Candida albicans* and *Aspergillus spp* [43,46,46]. Diagnosis includes reduced expression of CD18 in neutrophils (less than 5% of normal) accompanished by recurrent or persistent bacterial or fungal infections with leukocytosis (>25.000 leukocytes/mm^3 blood) and delayed cord separation. Because leukocytes express CD18 on their surface after 20 weeks of gestation, cordocentesis is performed to establish prenatal diagnosis [46,47,48]. Prolonged and continuous use of antibiotics decreases the frequency of infections, but does not eliminate the possibility of occurring severe episodes of infection. Therapy with recombinant human IFN-γ (rHUIFN) is relatively successful. During severe episodes of infection, it is recommended the infusion of granulocytes, followed by agressive antibiotic therapy. The curative treatment is transplantation of hematopoietic stem cells, recommended for all patients with severe forms of the disease or patients with the moderate form, with decrease in quality and expectancy of life [49,50].

LAD-2 is an autosomal recessive inheritance with mutation in the *FUCT1* gene, responsible to encode GDP-fucose transporter, that interferes with support of the intracellular GDP-fucose to the Golgi apparatus, abolished synthesis of syalil-Lewis (sLe^x) on the surface of phagocytes, which binds to E-selectin and P-selectin in the vascular endothelium [13]. The clinical presentation of LAD-2 is similar to LAD-1 features plus hh-blood group (Bombay phenotype), mental and growth retardation. Patients treated with oral fucose present correction of sLe^x expression in the surface of neutrophils with a reduced number of circulating neutrophils to near normal. Fucose replacement should be done cautiously because it is absorbed by leukocytes and erythrocytes, producing H antigens on the surface of red blood cells [51]. Since children with LAD-2 have high levels of anti-H antibodies, severe intravascular hemolysis may occur [43,46,47].

LAD-3 is an autosomal recessive inheritance associated with *KLINDLIN3* mutation, causing defects in regulation of Rap-1 activation of β-1-3 integrin of neutrophils, macrophages, lymphocytes, NK cells and platelets, compromising leukocyte adhesion to vascular endothelium and platelet aggregation [13]. The Glanzmann's thrombasthenia signs are observed in these patients, and clinical presentation of LAD-3 is similar to LAD-1, plus bleeding tendency [52,53].

9. RAC 2 DEFICIENCY

Neutrophils use a variety of proteins and signaling pathways such as GTPases (Rho, Rac and Cdc family), responsible for polymerization of actin cytoeskeletal regulation and intracellular signaling of neutrophils [1,14]. The Rac protein has two isoforms, Rac1 and Rac2, this last represents more than 96% of the Rac protein expressed in neutrophils. Rac 2 interacts with cytochrome b$_{558}$ and p67-phox, required for oxidative burst and has an important role in the dynamics of actin cytoeskeleton during rolling, chemotaxis, and phagocytosis. Mutations in *RAC2* results in a phenotype with characteristics common to chronic granulomatous disease, leukocyte adhesion deficiency and deficiency of β-actin [13,54]. Clinical manifestations of patients include leukocytosis, defective rolling by

GlyCAM-1 of L-selectin, mild to moderate adhesion, defects of neutrophlis chemotaxis, defects in phagocytosis and superoxide anion production. Transfusion of granulocytes and bone marrow transplantation are the best options of treatment for these patients [6,55].

10. β-ACTIN DEFICIENCY

β-actin deficiency is an autosomal dominant disease caused by mutations in the *ACTB* gene, causing defective actin polymerization in neutrophils and macrophages, compromising their motility [6,13]. Patients have recurrent bacterial infections involving skin and mucous membranes, which can progress to septicemia. Affected tissues are devoid of neutrophlis with poor wound healing, despite leukocytosis. Others reported changes are short stature and mental retardation. Prolonged and continuous use of antibiotics decreases the number of infections.

11. LOCALIZED JUVENILE PERIODONTITIS

Localized juvenile periodontitis is an autosomal recessive disorder caused by mutation of the *FPR1* gene, which encodes a chemokine receptor responsible for formylpeptide-induced chemotaxis [6,13]. The disease is characterized by periodontitis with loss of bone around molars and incisors teeth between 11 to 13 years old. In the United States, the prevalence is common among African American descendants. *Actinobacillus actinomycetemcomitans* is the common pathogen associated with periodontal infection. If the disease is observed in the early stage of life, treatment includes supportive surgical procedures in conjunction with antibiotic therapy [56,57,58].

12. PAPILON-LEFREVE SYNDROME

Papilon-Lefévre syndrome or palmoplantar hyperkeratosis with periodontitis is an autosomal recessive disorder caused by mutation in the *CTSC* gene, responsible for cathepsin C activation of serine proteases, located on chromosome 11q14.1-q14.3 [59,60,61]. Catepsin C is a lysosomal protease expressed in epithelial palmoplantar regions and granulocytes. The syndrome is estimated in $1\text{-}4/1\text{x}10^6$ individuals with inbreeding described in a third of the cases, characterized by severe periodontitis and palmoplantar keratoderma with loss of primary teeth around 4 years and permanent teeth around 14 years age [6,59]. Hyperkeratotic psoriasiform erythematous plaques may be present in elbows, knees and trunks. Skin infections, liver abscesses, pyelonephritis, anodontia, acro-osteolysis and malignant melanoma are relative common [13]. Other disorders include mental retardation, intracranial calcification (tentorial and chroid), nail dystrophy, sparse hair and palmoplantar hyperhidrosis. Immunological defects include a decrease of chemotaxis and phagocytosis of neutrophils and macrophages and T-cell lymphopenia [62,63]. Treatment of cutaneous manifestations include the use of emolient and keratolytic products and systemic retinoids, including acitretin and isotretinoin. Periodontis is difficult to control and treatment involves

extraction of primary teeth associated with systemic antibiotics and clearing of teeth. Antibiotic use is important to control active periodontitis to preserve teeth, bacteremia and liver abscess formation [59].

13. SPECIFIC GRANULES DEFICIENCY

Specific granules deficiency is an autosomal recessive disorder with mutations in the *CEBPE* gene, a myeloid transcription factor expressed during maturation of granulocytes [6,13]. It is characterized by the loss of specific or secondary granules during maturation of neutrophils. Specific granules stock proteins for the phagocytosis process, death and digestion of microbes; its absence determines decreased chemotaxis and occurrence of recurrent severe infections of skin and lungs by *Staphylococcus aureus, S. epidermidis, Pseudomonas aeruginosa*, enterobacteria *and Candida albicans.* The main clinical characteristic is increased susceptibility to pyogenic skin infections that persist for months, lung abscess and mastoiditis. Diagnosis can be made by peripheral blood smear, because neutrophils do not show specific granules, present bilobed nuclei, similar of Pelger Huet Syndrome. Aggressive antibiotic treatment and prophylaxis minimizes infectious complications. Another option is the transplant of hematopoietic cells [6].

14. SHWACHMAN-DIAMOND SYNDROME

Shwachman-Diamond syndrome is an autosomal recessive inheritance caused by mutation on the *SBDS* gene located on chromosome 7, characterized by pancytopenia, exocrine pancreatic insufficiency, chondrodysplasia, increased susceptibility to recurrent infections, leukemia and skeletal abnormalities. The *SBDS* gene is responsible for survival of granulocytic precursors and neutrophil chemotaxis [6,13,64]. This syndrome is the second most common cause of pancreatic insufficiency after cystic fibrosis and third cause of inherited bone marrow failure after Fanconi anemia and Blackfan-Diamond anemia. Its incidence has been estimated to 1/75,000 individuals [6]. Patients present in early childhood malabsorption, steatorrhea and growth retardation. Neutropenia is the most common hematologic abnormality, observed in 98% of patients, followed by anemia (42%), thrombocytopenia (34%) and pancytopenia (19%). Bacterial infections of respiratoty tract, otitis media, sinusitis, pneumonia, stomatitis, paronychia, osteomyelitis and bacteremia are common. Skeletal abnormalities are reported in more than 75% of patients, and more than 50% these patients have short stature with normal growth speed. Cognitive disorders and varying degrees of mental development are observed in 15% of patients. Development of severe cytopenia, myelodysplastic syndrome and acute myeloid leukemia are reported in 5-10% of cases. Death usually occurs from sepsis or malignancy [65,66,67]. Treatment involves use of antibiotics, and use of G-CSF in patients with Shwachaman-Diamond syndrome is less common.

15. CHRONIC GRANULOMATOUS DISEASE

Chronic granulomatous disease is a primary immunodeficiency of phagocytes, with X-linked inheritance or autosomal recessive inheritance [68]. The X-linked form affects $1/2,5 \times 10^5$ individuals with mutation in *CYBB* gene that's encoding the heavy chain of cytrochrome b_{558}, or gp91-phox (56% cases), an electron transport protein responsible of burst oxidative of phagocytes. These patients present severe and recurrent infections of the skin, respiratory system, gastrointestinal tract and adjacent lymphonodes; pancreas, bones, and central nervous system [69]. The major infectious agents are *Staphylococcus aureus,* gram-negative bacilli, *Aspergillus, Candida,* and *Nocardia* [70,71]. Persistence of microorganisms in phagolysosomes leads to the formation of granulomas that cause obstruction along the gastrointestinal or urinary tract. In the autosomal recessive form, affected genes include other components of the NADPH oxidase system; *NCF1* (adapter protein p47-phox, 33% cases); *NCF2* (activator protein p67-phox, 5% cases); *CYBA* (p22-phox, 5%); and *NCF4* (p40-phox) [13,72]. Patients with the X-linked form present severe infections in the first year of life, and patients with autosomal recessive forms tend to present less severe clinical manifestations, with late onset symptons. Oral ulcers and autoimmune manifestations are common in patients with X-linked form, and McLeod phenotype, which includes compensated hemolysis, acanthocysis and progressive degenerative neuromuscular disorders [73]. Diagnosis is based on clinical aspects of disease and laboratory evidence of defective oxidative burst. Laboratory diagnosis includes nitroblue tetrazolium test (NBT) and flow cytrometry with dihidrorodamin (DHR). Conclusive diagnoses include identifying the altered gene and mutation [74]. Prophylactic treatment of infections includes immunization and removing sources of pathogens. All patients need routine immunization and annual vaccine against influenza. Vaccines with atte.nued bacteria such BCG are contraindicated because of the risk of severe adverse reactions. Sulfamethoxazole+trimethoprim reduce in half the incidence of bacterial infections and itraconazole prevents fungal infections [68]. The use of rhuIFN-gamma reduces the relative risk of severe infections by 70%. Bone marrow transplantation is an alternative cure for CGD [75,76].

16. DEFECTS IN IL-12, IL-23/IFN-γ AXIS

IFN-γ is an cytokine produced by NK cells and activated T lymphocytes, which binds to a specific receptor with two subunits (R1 and R2) present on the surface of macrophages, with intracellular signaling with JAK1, with interactions with JAK2/STAT1, inducing production of IL-12. IL-12 acts on specific receptors with two subunits (β1and β2) and intracellular signaling by β1-TYK2 and β2-JAK2/STAT4 which induces synthesis and production of IFN-γ by TCD4 lymphocytes and NK cells. IL-12 is composed of two subunits, p35 and p40, formed IL-12p70. IL-23 is produced by activated macrophages, and have the common p40 subunit. Defects in this axis involving *IFNGR1, IFNGR2, IL12β, IL12IL23Rβ1* and *STAT1* result in increased susceptibility to mycobacteria and *Salmonella*. This group of diseases was previously called Mendelian Susceptibilty to Mycobacterial Disease (MSMD) [77,78,79,80]. Genetic complete defects in *IFNGR1* and *IFNGR2* (39% cases) cause complete deficiency of IFN-γ receptor type 1 and severe clinical phenotype [81,82]. This disease has an

autosomal and recessive inheritance with susceptibility to atypical mycobacteria (*Mycobacterium avium*, *M.kansaissii*, *M. szulgai*, *M. cheionae*, *M. abscessus*, *M. peregrinum*, *M. smegmatis*, *M. fortuitum*) and disseminated Calmette-Guérin (BCG) infection [79]. These patients are unable to control infections and the use of antibiotics and rhuIFN-gamma is ineffective [80]. In a partial defect of *IFNGR1*, patients present moderate clinical disease and late susceptibility to mycobacterial infections; rhuIFN-gamma is recommended in cases of refractory prolonged antibiotic therapy [82,83,84]. Partial and complete defects in IFNGR2 (4% cases) results in patients with clinical phenotype similar to defects observed in patients with complete and partial IFNGR1 defect. Defects in *IL12IL23β1* receptor (40% cases) involving T and NK cells, with IL-12 normal production, but lower IFN-γ syntesis, caused by autosomal recessive inheritance lead to susceptibility to mycobacteria, *Salmonella* and BCG infections [85,86]. Treatment includes aggressive antibiotical therapy, and refractory cases rhuIFN-gamma. Deficiency of IL-12p40 (9% cases) is an autosomal recessive inheritance with lower IFN-γ synthesis and higher susceptibility to mycobacteria, *Salmonella* and *Nocardia*; treatment includes agressive antibiotic therapy, rhuIFN-gamma and recombinant human IL-12 [87,88,89,90]. Partial and complete defect of *STAT1* (5% cases) are autosomal dominant or autosomal recessive,. Patients with partial forms exhibit susceptibility to mycobacteria and BCG infection, with good response to aggressive antibiotic therapy. However, patients with the complete form present increased susceptibility to mycobacteria, BCG and viruses that are refractory to antibiotical therapy and rhuIFN-gamma therapy [91,92].

17. HYPER-IGE SYNDROME

Hyper-IgE syndrome, Job syndrome or Buckley syndrome is a disease characterized by elevated IgE serum levels (>2000 IU/mm^3 blood), eosinophilia, lower neutrophils chemotaxis, lower production of IFN-γ, staphylococcal skin abscesses, eczema and recurrent pneumonia with formation of pneumatoceles. The incidence is estimated at 1/1,000,000 individuals with autosomal dominant or autosomal recessive inheritance [93,94]. Mutations of *STAT3* gene lead to autosomal dominant inheritance, whose patients present abnormalities in bones, lung cysts and interruption of Th17 development and IL-10 production [95,96,97]. Symptoms start in early life with skin infections by *Staphylococcus aureus* and *Candida albicans*, pneumonia and eczema [93]. Facial abnormalities are observed usually at 16 years of age and include facial asymetry, prominent forehead, deep-set eyes, broad nasal bridge, nasal tip meaty and mild prognathism [98,99]. Joints present hypermobility, bone fragility with recurrent pathological fractures that occur in 50% of patients, affecting long bones and ribs. Scoliosis is seen in 75% of patients; defects in teeth are the result of reduced reabsorption of roots of primary teeth and prolonged retention of deciduous teeth, preventing eruption of permanent teeth [13].

Mutation of *TYK2* gene leads to an autosomal recessive form of the disease. The *DOCK3* gene is responsible to exchange guanine nucleotide that induces reorganization of actin cytoskeleton, adhesion, phagocytosis, polarization and synapse formation [13]. Mutations in this gene lead to lymphopenia of T, B and NK cells, and increased susceptibility to herpes simplex, papillomavirus, molluscum virus, varicella zoster, leukemia of T cells and Burkitt

lymphoma, attributed to decreased activity of T CD8 cells. This autosomal recessive form gives rise to neurological complications due to viral infections [93,94,100]. Treatment include antibiotics, antifungals, lower doses of cyclosporine, IVIG and rhuIFN-gamma; however, only few patients often benefit from treatment. Bone marrow transplantation is not effective [93,94].

18. PULMONARY ALVEOLAR PROTEINOSIS

Pulmonary alveolar proteinosis is a disease characterized by the accumulation of lipoproteins between alveolar spaces, which interfere with the pulmonary gas exchange process, by *CSF2RA* gene mutation [13]. This disease has a prevalence of 0.37/100,000 individuals, predominantly males (3:1) with 80% of cases during third and fourth decades of life. Patients have defects in alveolar macrophage function, abnormal structures of surfactant protein, altered production of cytokines and abnormal expression of receptors to colony-stimulating factor granulocyte-macrophage in alveolar macrophages and pneumocytes type II [101]. Common symptoms are dyspnea and cough, fever, chest pain, and hemoptysis usually during lung infection. Laboratorial tests include arterial blood gases dosage, measurement of lactic dehydrogenase, surfactant proteins (A, B, D), chest radiography and computed tomography [102]. Conclusive diagnoses include bronchoalveolar lavage and transbronchial biopsy, although open lung biopsy is specific [103]. Treatment consists of lung lavage, bronchoscopic segmental or lobar and replacement therapy with G-CSF. Other treatment include corticoids, potassium iodide, streptokinase, and trypsin [104,105,106].

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