Phenocopies: Mimics of Inborn Errors of Immunity

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Abstract

A phenocopy is defined as a clinical non-inherited phenotype in an individual, with environmental induction, which is identical to the genetically determined phenotype of another. Until February 2017, the IUIS (International Union of Immunological Societies) reported in its classification 354 innate immunity errors and a final group (classification table IX) with conditions that are not part of the innate alterations and are called phenocopies. These are classified into two types, the associated with somatic mutations and those associated with auto-antibodies. The phenotypes that occur by any of the mechanisms mentioned are complex and varied. It is necessary to know the clinical manifestations of the pathologies classified in this group to enrich the possible differential diagnoses in individuals with suspected immunodeficiency.

Subject Areas

Allergy & Clinical Immunology, Immunology

Keywords

Phenocopies, Primary, Deficiency, Immunologic Deficiency Syndrome

1. Phenocopies of Inborn Erros of Immunity

A phenocopy is defined as a clinical phenotype in an individual, non-inherited, with environmental induction, which is identical to the genetically determined phenotype of another [1] [2]. Until February 2017, the IUIS (International Un-

ion of Immunological Societies) reported in its classification 354 innate immunity errors and a final group (classification Table IX) with conditions that are not part of the innate alterations and are called phenocopies. This group is divided into two categories, associations with somatic mutations and those associated with autoantibodies [3] [4] Table 1.

It is necessary for the first contact physician to know this type of pathologies that can occur at any stage of the patient's life, so that they are included within the repertoire of diseases to perform differential diagnosis. The most important characteristics to make a suspicion and confirmatory diagnosis of the modifications classified as phenocopies of innate immunity errors are described below.

2. Phenocopies Associated with Somatic Mutations

It is known as a mutation to an error in the genetic material of a cell, mutations can happen in somatic cells or germ cells. Once a somatic mutation happens, all cells derived from it will inherit that mutation. These types of mutations are not transmitted to the next generation [5] [6].

2.1. Autoimmune Lymphoproliferative Syndrome with Somatic Mutation in FAS (ALPS-sFAS)

Autoimmune lymphoproliferative syndrome (ALPS) (OMIM 601859/603909) is characterized by chronic evolution, lymphoproliferation not associated with malignancy and autoimmunity, accompanied by increased numbers of double negative T cells (DN, a/β CD4-CD8-) and elevated risk to develop malignant diseases in adult life. In about 70% of cases, the disease is caused by germinal mutations in components of the FAS pathway, mainly mutations in the TNFRSF6, CD95, APO1 gene (ALPS type 1a) [7]. In other cases of ALPS the mutations are in genes encoding ligand FAS (ALPS type 1b), caspases 8 and 10 (ALPS type II), or NRAS (ALPS type IV). These alterations are classified within group IV of the IUIS classification that includes diseases with immunological deregulation and autoimmune syndromes.

Table 1. Phenocopies of inborn errors of immunity, IUIS classification [3].

Associated with somatic mutations	Associated with auto-antibodies
ALPS-sFAS. Somatic mutations in TNFRSF6	Chronic mucocutaneous candidiasis. (Isolated or with APECED syndrome). AutoAb to IL-17 and/or IL-22
RALD (RAS-associated autoinmuneLeukoproliferative disease). N-RAS GOF, K-RAS GOF	Adult onset immunodeficiency with susceptibility to mycobacteria. AutoAb to INF-γ.
Cryopyrinipathy (Muckle-Wells/CINCA/NOMID-like). NRLP3	Recurrent skin infections. AutoAb to IL-6.
	Pulmonary alveolar proteinosis. AutoAbto GM-CSF
	Acquired angioedema. AutoAb to C1 inhibitor.
Hypereosinophilic syndrome due to mutations in STAT5b. STAT5b GOF	Atypical Hemolytic Uremic Syndrome. AutoAb toFactor H.
	Thymoma with hypogammaglobulinemia (Good syndrome). AutoAbto various cytokines.

Lymphoproliferation is the most common clinical manifestation and has chronic evolution (>6 months), and is also accompanied by lymphadenopathy, hepatomegaly or splenomegaly. Autoimmunity is the second manifestation in frequency, usually affects 70% of patients, the presentation includes cytopenias such as autoimmune hemolytic anemia and autoimmune mediated thrombocytopenia, and autoimmune neutropenia is less common [8]. Table 2 shows the revised diagnostic criteria of ALPS [9] [10].

The phenocopy of these innate immunity errors refers to the somatic mutation in FAS (ALPS type III), initially it had been described that the alteration could present clinically without the classic manifestations or incompletely [11]. Dowdell *et al.*, Analyzed 15 individuals with type III ALPS and compared them with 16 patients with ALPS type Ia, the clinical evolution of the patients was similar, however there was less incidence of splenectomy and a lower lymphocyte count in patients with somatic mutation. The characteristics of the lymph node biopsy of 5 patients with somatic mutation were the classic lymphadenopathy associated with ALPS, 3 patients showed in the biopsy, cell augmentation in cells with positive S-100 protein similar to what is expected in Rosai-Dorfman disease. The remaining 5 patients had poor specific changes with follicular and reactive parafolicular hyperplasia. The average age of presentation in type III was 10 years (3m-48a) and type I 5 years (0m-53a). Although defects in apoptosis were found, being less pronounced in patients with type III ALPS compared to Ia, no statistical significance was found [12].

This findings demonstrate that clinically the presentation of ALPS is the same regardless of the mutation found, however the diagnosis of the phenocopy of this inborn error of immunity must have the identification of the alteration as a probable type III ALPS and try to find the somatic mutation in an individual in whom the germ mutations have not been found.

Table 2. ALPS Revised criteria, report from the 2009 NIH International Workshop [9].

Required
1) Chronic lymphadenopathy (>6 months) without malignancy, non-infectious or splenomegaly or both
2) Elevation of DN cells, CD3 + TCR$\alpha\beta$ + CD4-CD8- (≥1.5% of total lymphocytes or 2.5% of CD3+ lymphocytes)
in the context of normal or elevated lymphocyte count

Accessories
Primary
1) Lymphocyte defective apoptosis (in 2 different trials)
2) Somatic or germline mutation in FAS, FASLG, or CASP10
Secondary
1) Elevation of sFASL plasma levels (>200 pg/mL) or elevated Interleukin-10 plasma levels (>20 pg/mL) or elevated B12 vitamin
serum levels (>1500 ng/L) or elevated interleukin-18 plasma levels (>500 pg/mL)
2) Typical immunohistological findings in a review by an expert hematopathologist
3) Autoimmune cytopenias (hemolytic anemia, thrombocytopenia or neutropenia) and elevated levels of immunoglobuline G
(polyclonal hypergammaglobulinemia)
4) Family history of lymphoproliferation without malignancy, non-infectious with or without autoimmunity

The definitive diagnosis is realized with the presence of the 2 required criteria plus a primary accessory criterion.
A probable diagnosis is based on the presence of 2 required criteria and a secondary accessory criterion.

Martinez-Feito *et al.* reported a somatic mutation in FAS and a germinal mutation in CASP10 in the same patient that met the full criteria for ALPS [13], related to what was observed in the case report presented by García-García *et al.*, in a 55-year-old patient with chronic lymphadenopathy as the only manifestation and only somatic mutation of FAS that did not require treatment, [14] we can argue that sometimes two mutations may be necessary to cause the complete manifestation of the syndrome.

More than half of patients with ALPS need immunosuppressive treatment for manifestations of autoimmunity, high-dose systemic steroid schemes are needed for short cycles [15]. The use of medications such as mycophenolatemofetil, azathioprine, methotrexate, 6-mercaptopurine or sirolimus has also been documented, although they are not compatible to control the disease by themselves, so hematopoietic progenitor cell transplantation can be alternative [16] [17]. Rituximab has been used for patients with cytopenias refractory to treatment, although it is advised that the risk of prolonged hypogammaglobulinemia must be assessed in all patients [18].

2.2. RAS-Associated Autoimmune Leukoproliferative Disorder

The RAS-associated autoimmune Leukoproliferative disorder (RALD) is a pathology not associated with malignancy, initially identified in individuals with ALPS [19]. The main difference is that there is not an elevation of DN T cells (α/β CD4-CD8-) or serum vitamin B12 alterations, the germinal or somatic mutations characteristic of ALPS are absent. Absolute or relative monocytosis is the definitive characteristic of RALD [20].

RAS proteins are essential components in cellular signaling of the immune system, TCR stimulation causes rapid activation of RAS and this protein regulates activation pathways of T cells [21] [22].

RALD is caused by gain of function mutations in the RAS family proteins (NRAS and KRAS) and shares clinical characteristics with ALPS without meeting the definition of DN T cell elevation in peripheral blood. This pathology is characterized by autoimmunity, lymphadenopathy, splenomegaly, cytopenias and monocytosis. Somatic mutations in NRAS and KRAs have been found in myeloid malignant pathologies and other types of cancer [23].

The importance of KRAS is that it is enzymatically active when a GTP is found and activates various signaling factors. For inactivation a hydrolysis of GTP to GDP is performed. Gain-of-function mutations eliminate the intrinsic inactivation ability. NRAs, another member of the RAS family, also play an important role in intracellular signaling pathways, as well as proliferation and apoptosis. Germ mutations of KRAS produce cardio-fascio-cutaneous, Costello and Noonan syndromes [24] [25].

The clinical presentation in individuals in whom the somatic mutation without germinal mutation of KRAS is the symptomatology of ALPS, although with predominant autoimmune cytopenias and hepatosplenomeomegaly, however, this pathology has special characteristics. Patients present monocytosis as a dif-

ferential clinical feature [26]. Therefore, it is also necessary to establish a differential diagnosis with juvenile myelomonocytic leukemia (JMML) [20]. NF1 and RAS family mutations have been found in these leukemia cells, so even in this pathology there may also be somatic mutations of KRAS, some authors propose that somatic mutation can occur in stages prior to the onset of malignant hematology disease [27].

Wang *et al.* studied the clinical manifestations of patients with somatic mutation in NRAS. They report in terms of frequency the presence of rash, arthritis and thrombocytopenia, initially these patients were studied as patients with early onset Systemic Lupus Erythematosus (SLE) and stood out from the study group because they did not present typical characteristics of the disease [28]. The clinical manifestations in general terms do not differ from the mutations in KRAS.

The treatment of RALD includes medications such as systemic steroids, cyclosporine, and azathioprine and has been successful in patients presenting with refractory cytopenias with rituximab [29].

2.3. Cryopyrinopathy

The cryopyrin-associated periodic syndromes (CAPS) are a group of diseases characterized by fever, systemic inflammation and skin rash [30], these inborn errors of immunity are within the classification in group VIIa, they are heritable pathologies and have been identified in mutations with gain-of-function in NLRP3 and NLRP12. NLR contains a pyrin domain such as NLRP3 and/or caspase activation domains (CARD), which promotes its self-assembly, some NLRs form multiprotein complexes called inflammasomes, which protect the cell from injuries as well as regulate homeostasis. The gain-of-function mutations in NLRP3 cause hyperactivation of cryopyrininflammasome and thus cause disease manifestations [31] [32].

The phenocopy of this inborn error of immunity is a somatic mutation in NLPR3, which makes the disease not inheritable but with a clinical behavior phenotypically equal to the germline mutation. The clinical manifestations of this pathology have been reported in syndromes similar to Muckle-Wells, chronic infantile neurological-cutaneous-articular syndrome (CINCA) and neonatal multisystemic inflammatory disease (NOMID). All subtypes have cutaneous, musculoskeletal, ocular manifestations and central nervous system involvement to varying degrees, although the most frequent initial manifestation in any of the syndromes is the urticarial rash [33]. In addition, patients presenting with fever, myalgia, arthralgia, headache, conjunctivitis, keratitis, sterile meningitis. Symptoms are triggered by exposure to cold (described at temperatures below 72°F for more than 30 minutes), exacerbations have a chronic course and vary from 1 to 3 days. Table 3 shows the characteristics that can help differentiate these syndromes [31] [34].

In laboratory studies, patients present with leukocytosis and during exacerbations, neutrophiliais found, there is a little elevation of acute phase reactants.

Table 3. Cryopyrinopathy clinical features for differential diagnosis. Modified from Booshehri LM, Hoffman HM. CAPS and NLRP3. J Clin Immunol. 2019; 39(3): 277-86 [32].

	Familial cold auto-inflammatory syndrome (FCAS)	Muckle-Wells Syndrome	CINCA/NOMID
Clinical characteristics	Urticarial rash, fever, fatigue, chills, arthralgia, myalgia, conjunctivitis, keratitis, headache.	Urticarial rash, fever, fatigue, arthralgia, myalgia, arthritis, conjunctivitis, keratitis, uveitis, sensory hearing loss, headache.	Urticarial rash, fever, fatigue, arthralgia, myalgia, distal femur overgrowth, conjunctivitis, keratitis, uveitis, papilledema, sensory hearing loss, headache, aseptic meningitis, intracranial hypertension, developmental delay.
Patterns of exacerbations	12 - 24 h	1 - 3 days	1 - 3 days

Skin biopsy may show edema and neutrophilic infiltrate in the dermis [31]. The findings in imaging studies such as magnetic resonance, the IRM of the central nervous system have shown a decrease in the T2 signal in the cochlea and brain, which is related to the loss of sensory hearing in these patients [35] [36].

The definitive diagnosis of this phenocopy is made in individuals with germline mutations negative to NLRP3 with clinical manifestations characteristic of these syndromes. When sequencing is performed in this group of patients, some degrees of somatic mutations have been reported for NLRP3 in up to 15% of patients [37] [38].

Secondary renal amyloidosis is one of the main complications of these pathologies and the treatment is aimed to reducing the inflammation that causes the hyperactivity of the inflammasome [39].

The treatment consists in blocking the action of IL-1β that is elevated, with medications such as anakinra, rilanocept, canakinumab, although they have been associated with an increased risk of infections, particularly tuberculosis [40] [41] [42] [43] [44]. Despite these treatments, patients have a significant decrease in the quality of life, rated by decrease in EuroQol five-dimensional questionnaire (0.769 out of total score of 1, N = 14) [45].

Various ways to block the activation of NLRP3 with s drugs such as glyburide, dapansutrile, 3 - 4 methylene dioxy-β-nitrostyrene, oridine, tranilast and compound CY-09 are currently under investigation, the latter directly blocking the ATP binding site of NLRP NATCH, thus inhibiting its ATPase action, oligomerization and activation.

2.4. Hypereosinophilic Syndrome Due to Somatic Mutations in STAT5b

STAT are cytosolic proteins involved in the signaling of type I and II cytokine receptors. Seven proteins of this family have been identified (STAT1, 2, 3, 4, 5a, 5b and 6). Germ or somatic mutations affect the structure and function of the protein causing immunodeficiency and autoimmunity. Somatic gain-of-function mutations in STAT3 and STAT5 have been described frequently in lymphoma and leukemia [46] [47] [48]. Altered transcriptional activity of STAT5b causes

immunodeficiency and dysfunction, this pathology is classified in group IIb of the IUIS, which includes combined immunodeficiencies with syndromatic characteristics. The alteration manifests itself in short stature due to insensitivity to growth hormone, dysmorphia, eczema, lymphocytic interstitial pneumonitis and autoimmunity [49].

Germline gain-of-function mutations in STAT3 manifest with developmental delay, repetitive respiratory tract infections, susceptibility to non-tuberculous mycobacteria, multiorgan autoimmunity such as autoimmune enteropathy, subclinical hypothyroidism with positive anti-TPO antibodies, sicca syndrome or subsequent uveitis, anemia and autoimmune thrombocytopenia. The treatment is directed to complications and immunomodulatory medications are used for autoimmune pathology [50]. What we know about somatic mutations is that it manifests clinically with migratory annular erythema, persistent urticaria, diarrhea and eosinophilia in laboratory studies. The shared mutation of the reported patients is STAT5 N642H, a single nucleotide variant. In murine models, the increased activity of STAT3 causes an increase in the sensitivity of IL-3 and an increase in the production of thymic stromal lymphopoietin, which may explain dermatitis-like manifestations. The manifestations do not have a good response with conventional treatment and hematopoietic progenitor cell transplantation has been performed although with post-transplant complications [51].

3. Phenocopies Associated with Auto-Antibodies

This group includes the immunological alterations that cause the production of autoantibodies against various cytokines and complement activation regulatory factors. The diseases in the current classification are analyzed below.

3.1. Chronic Mucocutaneous Candidiasis (CMC) (Isolated or with APECED Syndrome)

The presence of autoantibodies against IL-17 and/or IL-22 causes manifestations in this pathology. Interleukins 17 and 22 are important for the immune response in the mucous membranes. IL-17 also induces neutrophil infiltration, activation and survival, in addition to cytokine expression and IL-22 production. IL-22 is an interleukin secreted by several cells such as CD4+, CD8+, NKT, $\gamma\delta$ T cells and CD4+ Th17. It acts by altering the expression of genes related to the defenses of innate immunity to bacteria, including β-defensins, promotes chemokine expression and releases IL-6 and TNF [52].

APECED also called autoimmune polyglandular syndrome type 1 (APS-1) (OMIM240300) is a monogenic disease, caused by biallelic mutations in the autoimmunity regulator (AIRE), is classified as a group IV immunodeficiency of the IUIS,the patients presentwith hypoparathyroidism, hypothyroidism, adrenal insufficiency, diabetes, gonadal insufficiency in addition to chronicmucocutaneous candidiasis [53] [54]. The production of antibodies against IL-17 and IL-22 is a characteristic of these patients in addition to the specific organ antibodies [55] [56]. There is also aassociation between the presence of antibodies against

IL-17A and the predisposition to CMC in patients with APECED [57].

The presence of CMC can also be isolated, it has been shown that these patients have decreased production of IL-17 and low proliferation of IL-17 CD4+ with the stimulation of Candida species, these findings do not differ from individuals who present APECED [58] [59]. Patients presenting with autoantibodies against IL-22, have the same manifestations. These autoantibodies are predominantly IgG4 [60].

Due to the immunopathology of this condition, immunosuppressive treatment is indicated for CMC cases in the context of APECED. The use of cyclosporine A has related to reverse pancreatic insufficiency, keratitis and alopecia. Other medications used with reversal of CMC lesions are tacrolimus, mycophenolate and prednisone [61] [62].

3.2. Adul-Onset Immunodeficiency with Susceptibility to Mycobacteria

Susceptibility to non-tuberculous mycobacteria is a characteristic of this disease in which the INF-ɣ pathway is affected by the presence of autoantibodies that block its effect [63]. INF-ɣ is mainly produced by Th1 cells, the activation of its receptor (INF-ɣR) phosphorylates and activates molecules such as STAT1. [64] Some studies have shown that the ability of interferon inhibition by these autoantibodies is more important than the concentration to determine the predisposition to the disease, besides there is a heterogeneity between the types of autoantibodies in each individual [65] [66].

One of the mycobacteria found in these patients is *Mycobacterium abscessus*, with fast growing, and in terms of slow growth *Mycobacterium avium complex* (MAC). Additionally, patients with a history of chickenpox virus (VZV) infection have reactivation such as herpes zoster and salmonellosis. It is reported in a smaller percentage of patients with fungal coinfection.

Cervical lymphadenopathy is the most frequent clinical presentation although bones and joints with osteomyelitis and arthritis are also affected. Dermatological manifestations in the form of a pustular rash could happen. In laboratory studies, patients have elevated CRP and ESR during the infectious period in addition to leukocytosis. Despite intensive antibiotic treatment, more than half of the patients will continue with persistent infection, in patients with this characteristic the duration of treatment can vary from 206 to 1439 days [67] [68].

The use of medications such as cyclophosphamide or rituximab significantly decreases the serum level of autoantibodies although have been associated with persistent infection [69].

3.3. Recurrent Skin Infection

IL-6 has important pleiotropic functions in hematopoiesis and cell regeneration, the increase in IL-6 leads to the constant activation of STAT3 which increases the expression of interleukin, so they are closely related. Its receptor (IL-6R) is an example of a soluble agonist receptor [70]. After IL-6 is synthesized in the in-

itial stage of inflammation, it is transported to the bloodstream along with the elevation of CRP, serum amyloid, fibrinogen, haptoglobin and $a1$-antitrypsin [71]. The presence of autoantibodies against IL-6 inhibits their action and therefore clinical manifestations couldoccur by the poor activation of the STAT3 pathway. It is common the presence of two or more episodes of staphylococcal skin infection. In the complementary laboratory studies, are not associated with elevated PCR [72]. It is not known exactly why the loss of self-tolerance in some individuals causes the formation of these autoantibodies. This phenomenon has also been studied in murine models in which it has been shown that IL-6 has an influence on metabolism and that along with other risk factors such as age and diet, the presence of autoantibodies against Il-6 is related with obesity, dyslipidemia and impaired glucose metabolism. In humans it has been documented that the presence of these autoantibodies is 2.5 times higher in individuals with type 2 diabetes compared to healthy ones [73]. The presence of autoantibodies against IL-6 has also been reported in patients with APECED or thymoma but their functions in these pathologies are stabilizers of interleukin and not responsible for clinical manifestations. In healthy individuals, the presence of autoantibodies against IL-6 can be found in up to 0.1% to 9% of the population [74] [75].

The treatment goal in this phenocopy is avoiding the complication of staphylococcal infection with early detection and timely antibiotic treatment. It has been observed that some patients did not need prophylactic antibiotic treatment to avoid the risk of infection [72] [76].

3.4. Pulmonary Alveolar Proteinosis (PAP)

This pathology is characterized by accumulation of surfactant factor in macrophages and alveoli which culminates in the alteration in the gas exchange. The pathophysiological mechanism is explained by the poor maturation of the alveolar macrophages secondary to the poor signaling of GM-CSF. In 90% of adult patient cases there is a decrease in the availability of this factor due to autoimmunity [77] [78]. Neonatal PAP is produced by the mutation of genes required for the adequate formation of surfactant factor, thus the phenocopy of this pathology is due to the formation of antibodies against FEC-GM.

The autoimmune form occurs in adults between 40 and 50 years old with nonspecific symptoms such as dyspnea and productive cough, due to the predisposition to infections these patients may present fever although it may also be not associated with infection. One third of patients may present asymptomatic although alterations in chest imaging studies can be detected at the same time [77].

One of the main alterations in the laboratory tests is the alteration in the diffusion of carbon monoxide (DLCO) [79]. High resolution pulmonary tomography is very useful for the diagnosis where the crazy-paving and ground glass pattern has been described. The definitive diagnosis is made by pulmonary biopsy and/or bronchoalveolar lavage (BAL) [80]. When they are available, the

determination of autoantibodies against GM-SCF can be performed to support the differential diagnosis [81]. The BAL fluid shows an milky aspect due to high protein content, acellular and basophilic dense oval bodies can be observed in electron microscopic vision. Histopathology shows eosinophilic and acellular, dense airways material with minimal interstitial inflammation. One of the complications that can occur in this pathology is late interstitial lung disease [82].

The treatment consists of total pulmonary lavage that can be efficient for a period of 15 months in 66% of patients [83] [84]. The administration of recombinant subcutaneous or inhaled FEC-GM has shown improvement in patient oxygenation [85] [86]. Treatment directed against autoimmunity includes steroid treatment for patients with concomitant connective tissue disease. Rituximab has been used as therapy for patients with moderate to severe disease although there is insufficient evidence to support its use routinely [87].

3.5. Acquired Angioedema

The C1 inhibitor (C1-INH) belongs to the serine protease inhibitor protein superfamily. The mutation in the *SERPING1* gene leads to a decrease in serum levels or a decrease in inhibitor functionality, this results in the loss of regulation of factor XIIa and calicrein enzymes culminating in the overproduction of bradykinin [88]. This innate error corresponding to Hereditary Angioedema (HAE) and it is classified within group VIII of the IUIS that corresponds to complement deficiencies. A percentage of patients present the clinical characteristics without presenting a genetic mutation, this form of the disease is called Acquired Angioedema (AAE) and one of the main causes is the pharmacological one due to the intake of angiotensin converting enzyme inhibitors. The phenocopy we will address corresponds to the presence of autoantibodies against C1-INH which causes the same disease phenotype but with a different immunopathological mechanism [89].

The inhibitory effect of the IgG-like antibody is mediated by the Fab region, the binding of C1-INH with the autoantibody can continue to react with proteases but the complex becomes very unstable [90]. This kind of autoantibodies has been found in patients with Systemic Lupus Erythematosus (SLE) although not related to manifestations other than those of the disease. The presence of this autoantibodies is related with the duration of disease activity [91].

Table 4 shows the useful clinical data for an adequate differential diagnosis in patients with angioedema and in whom this phenocopy is suspected [92].

The evaluation of complement fractions patterns is essential for the diagnosis. Table 5 shows the expected patterns for hereditary and acquired angioedema. [89] As can be seen, what defines this phenocopy is the presence of autoantibodies against C1-INH.

The treatment consists of administering purified plasma C1-INH or icatibant (bradykinin inhibitor), although due to the presence of antibodies it has been shown that higher doses of C1-INH may be necessary [93]. Although long-term prophylaxis with patients with more than one crisis of angioedema per month

Table 4. Differential diagnosis of angioedema and clinical characteristics [92] [94].

	Mediated by mast cells	Bradykinin-mediated.	
		Acquired	Hereditary
Symptom onset rate	Minutes	Hours	Hours
Average age of disease onset	Anyone	30 - 60 years old	0 - 20 years old
Site affected	Face, neck	Lips, tongue, uvula, upper respiratory tract	Face, extremities, upper respiratory tract, gastrointestinal tract
Hives	Yes	No	No
Family history	No	No	Yes
Drugs related	NSAID	Angiotensin Converting Enzyme inhibitors, Angiotensin Receptor Blockers, gliptins, sacubitril	Angiotensin Converting Enzyme inhibitors, estrogens
Antihistaminic response	Adequate	Without response	Without response

Table 5. Complement patterns and phenotypes of C1-INH deficiency [92].

Diagnosis	C1-INH	C1-INH function	C4	C1q	Autoantibodies against C1-INH
HAE wit C1-INH deficiency	Low	Low	Low	Normal	Absent
HAE type 2	Normal	Low	Low	Normal	Absent
AAE Type1	Low	Low	Low	Low	Absent
AAE Type2	Low/Normal	Low	Low	Low	Positive

can be performed with tranexamic acid three times a day. The use of ecallantide (plasma kallikrein inhibitor) can improve the course of the disease since there is no union of the drug with the autoantibodies [94]. The use of rituximab in these patients is reserved for cases without detection of autoantibodies against C1-INH and without underlying pathology. It is not known whether it is useful for reducing the risk of autoimmunity or lymphoproliferative disease [95] [96].

Patients presenting with angioedema crisis in the context of a disease such as SLE have improved with the administration of methylprednisolone pulses in 3 consecutive days in addition to maintenance therapy for the underlying disease [97].

3.6. Atypical Hemolytic Uremic Syndrome (a-HUS)

Factor H is a glycosylated plasma protein that has an important role in regulating the alternative complement pathway, acting in the fluid phase and on the cell surface. The absence of this factor produces spontaneous activation of the alternate pathway. Phenocopy of this deficiency is caused by the production of autoantibodies against factor H [98] [99].

The incidence of this pathology is very low, it is estimated 1 - 2 cases per mil-

lion population, there is no predominance of age. The prognosis is bad and a quarter of the patients develop kidney disease after the onset of the disease, they will also have ischemic symptoms in the CNS, cardiovascular and respiratory system, skin manifestations, skeletal muscle and in the gastrointestinal tract [100].

The diagnosis of a-UHS requires the following findings: 1) microangiopathic hemolytic anemia (hemoglobin < 10 g/dl) with direct negative Coombs test, elevation of lactate dehydrogenase (DHL), decrease of serum haptoglobin with peripheral blood schistocytes, 2) thrombocytopenia (<150,000 cell/mm^3), 3) acute kidney injury [101]. Patients require evaluation of the complement pathway, at least with serum levels of C3, factor H, I and B in addition to autoantibodies against factor H [102].

The treatment consists of supportive measures for ischemic complications or renal failure. Plasma exchange is one of the most used therapies although it does not resolve the alteration in the complement pathway. Eculizumab, an IgG monoclonal antibody that binds to the C5 portion, has become the preferred therapy as it decreases the risk of recurrence. Plasma treatment is not currently recommended unless eculizumab is not immediately available [103] [104]. The use of medications such as steroids, azathioprine, cyclophosphamide, rituximab, has been successful in reducing recurrences although the duration of treatment may be up to one year [105] [106].

3.7. Thymoma with Hypogammaglobulinemia (Good Syndrome)

Thymomas are rare thymic epithelial tumors, the age of presentation varies from 40 to 60 years old and they are rare in the pediatric population. These tumors frequently cause paraneoplastic syndromes with autoimmunity. Bone marrow involvement manifests as pure red cell aplasia and pure B cell aplasia, the latter may be the cause of some forms of Good syndrome presentation, although another potential mechanism of predisposition to infections is the presence of autoantibodies against various cytokines and this characteristic is what defines this phenocopy [107] [108].

The initial clinical manifestations may be due to thymoma such as dysphagia, cough, dysphonia and vena cava syndrome that are related to the size of the tumor. Characteristically, these patients may present with repeated infections and it is common to find manifestations of autoimmunity, of these pathologies the most frequently found relationship is with myasthenia gravis [109] [110] [111].

Laboratory studies show the absolute decrease of B cells and serum immunoglobulin values, patients with advanced stages of thymoma, also show a decrease in the CD3+ CD4+ lymphocyte count. It is common that bronchiectasis can be seen as a pulmonary complication in chest imaging studies [107].

The treatment is aimed at neoplasia, with timectomy, radio and chemotherapy, however patients require treatment with intravenous immunoglobulin substitute for hypogammaglobuinemia. Each patient should be individualized to determine the need for prophylactic antimicrobial treatment [112]. Immunosup-

pressants and monoclonal antibodies such as rituximab and tocilizumab have been used for thymoma-associated autoimmune syndromes after timectomy, since in some patients despite surgery they persist with autoimmunity manifestations [113].

4. Conclusion

The clinical manifestations presented by patients with phenocopies are indistinguishable from those presented by inborn immunity errors. The diagnosis of phenocopies is established once the genetic alteration in the germ cells of an individual with the clinical characteristics of the suspected pathology has been ruled out. It is necessary to recognize these clinical phenotypes to make an adequate differential diagnosis in patients in whom immunodeficiency is suspected.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations

AAE: Acquired angoedema

AIRE: Autoimmunity regulator

ALPS: Autoimmune lymphoproliferative syndrome

APECED: Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy

a-HUS: atypical hemolytic uremic syndrome

CAPS: Cryopyrin-associated periodic syndrome

CINCA: Chronic infantile neurological-cutaneous-articular syndrome

CMC: Chronic mucocutaneous candidiasis

CRP: C-reactive protein

FCAS: Familiar cold auto-inflammatory syndrome

HAE: Hereditary angioedema

IUIS: International Union of Immunological Societies

NOMID: Neonatal multisystemic inflammatory disease

PAP: Pulmonary alveolar proteinosis

RALD: RAS-associated autoimmune leukoproliferative disorder

SLE: Systemic Lupus Erythematosus