ORIGINAL RESEARCH PAPER
Volume - 13 | Issue - 12 | December - 2024 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

COPA SYNDROME: A RARE IMMUNEDYSREGULATORY DISEASES

Rheumatology

Raghavendra M Junior Resident, Department Of Paediatrics, Indira Gandhi Institute Of Child Health, Bangalore, India

Anil Kumar Tennelli Assistant Prof. Department Of Paediatrics, Indira Gandhi Institute Of Child Health, Bangalore, India

ABSTRACT

COPA syndrome is a rare inborn error of immunity that lead to immune dysregulation and autoimmunity, it is an autosomal dominant disorder characterized by variable expressivity with mutations in the COPA gene clinically manifest as recurrent fevers starting at an early age, interstitial lung diseases, and polyarthritis .Copa syndrome is autosomal dominant with variable expressivity and results from mutations affecting a narrow amino acid stretch in the COPA gene-encoding COPα protein. Patients with these mutations typically develop arthritis and interstitial lung. Immunologically Copa syndrome is associated with autoantibody development, increased Th17 cells and pro-inflammatory cytokine expression including IL-1β and IL-6. Insights have also been gained into the underlying mechanism of Copa syndrome, which include excessive ER stress owing to the impaired return of proteins from the Golgi, and presumably resulting aberrant cellular autophagy. As such it represents a novel cellular disorder of intracellular trafficking associated with a specific clinical presentation and phenotype. . To contribute to the knowledge of this rare disease, we present a case report.

KEYWORDS

Arthritis , interstitial lung disease, autoimmunity , primary immunodeficiency.

INTRODUCTION:

Typically, pediatric autoimmune diseases affect non-immune tissues, such as joints, skin and kidneys as a feature of misdirected immunity. Other common autoimmune targets in children include endocrine organs (e.g., type 1 diabetes) and hematologic cells themselves (e.g., immune-mediated cytopenias). However, pulmonary disease represents a relatively rare manifestation of immune dysregulation and autoimmunity in children and is seen in only a small number of phenotypic and genotypic conditions. The existence of immune-mediated pulmonary hemorrhage in children therefore points toward the presence of an underlying novel immune dysregulatory syndrome. Genetic immune dysregulatory syndromes are classified by the International Union of Immunological Societies (IUIS) as primary immunodeficiency diseases [1]

A recently identified novel autosomal dominant syndrome consisting of autoimmune lung, joint, and kidney disease in pediatric patients that is caused by mutations in the coatomer associated protein subunit alpha (COPα) gene (COPA; [2,3]. This "Copa syndrome" is caused by immune dysregulation, resulting in diffuse alveolar hemorrhage or interstitial lung disease, arthritis, and renal disease. COPα is part of the coatomer protein complex I (COPI) and helps to mediate retrograde movement of vesicles from the Golgi to endoplasmic reticulum (ER). These cellular processes were not previously recognized as causes of immune-mediated disease. Thus, Copa syndrome promises to yield important new insights concerning the role of intracellular trafficking in immune regulation and further mechanistic study will hopefully give rise to new therapeutic strategies to combat immune dysregulation. Interestingly COPA is expressed in all cell types while the clinical presentations are limited to pulmonary, joint, and renal tissues. Presumably it may be that these tissues are either more sensitive to the mutation and its impact on intracellular traffic, or they are more sensitive to the resulting pro-inflammatory environment which these mutations induce.

Here we present a cases of COPA syndrome presented to us in the age group of 2 year.

Case Report :

A Five-year-old female child born to nonconsanguineous married couple, presented with recurrent fevers, polyarthritis, and failure to thrive since the age of 2. On examination, the patient displayed clubbing in all fingers, generalized wasting, camptodactyly, bilateral lung crepitations, tenderness and swelling in all joints, and multiple contractures. On lab investigations inflammatory markers were elevated, ANA -3+, PID panel was normal. Xray of joints suggestive of erosion and deformity, HRCT chest suggestive of interstitial lung disease likely NSIP [4,5,6].

Whole exome sequencing indicated a diagnosis of COPA syndrome, revealing heterozygous missense variations in exons 23 and 9 of the COPA gene. The child was subsequently started on a treatment regimen that included a JAK inhibitor, steroids, and methotrexate.

DISCUSSION:

COPA syndrome is a relatively new genetic disorder characterized by immune dysregulation and is often underdiagnosed. In our case, as in previous reports, the disease onset occurred in early childhood with similar manifestations. Copa syndrome is a hereditary immune dysregulatory primary immunodeficiency resulting from mutations in the COPA gene and is listed in the most recent IUIS classification document as such as well as in OMIM [7,8].

Copa syndrome is inherited in an autosomal dominant pattern with variable penetrance. Patients with Copa syndrome develop pulmonary symptoms (most frequently pulmonary hemorrhage), arthritis, and renal disease. Most present early in life with 76% exhibiting signs and symptoms of disease under age of 5 years of age. The most common presenting symptoms include cough and tachypnea with some patients requiring supplemental oxygen at a young age. A female predominance for penetrance appears to existThis case report shows the common clinical and investigation profile of COPA syndrome case admitted to IGICH hospital.

Immune Dysregulation

Copa syndrome is marked by immune dysregulation, which can present in various forms. Approximately 80% of patients develop a positive ANA titer. Homogenous, speckled, and diffuse patterns of ANA staining have all been reported (with titers measured as high as 1:1,280). Other autoantibodies that may be present include both cytoplasmic anti-neutrophil cytoplasmic antibiody (cANCA) and perinuclear anti neutrophil cytoplasmic antibody (pANCA), anti-myeloperoxidase antibodies, anti-proteinase 3 antibodies, and rheumatoid factor antibodies. The presence and titers of antibodies vary with time and disease activity. However, no single autoantibody has yet emerged as a marker of disease severity, disease activity or disease progression. The full spectrum of autoantibodies in Copa syndrome is presently unknown, but is being pursued through multiple antigen screening approaches. Patients also often have elevated levels of serum markers of inflammation, including C-reactive protein and erythrocyte sedimentation rate.

Pulmonary Disease

Pulmonary disease is universally present in known patients affected by Copa syndrome. Patients develop progressive lung disease with worsening pulmonary function. Pulmonary function testing demonstrates restriction with a symmetrically low forced vital capacity and forced expiratory volume in the first second. Plethysmography reveals a low total lung capacity, and when tested, diffusion capacity of carbon monoxide is low. The two most common

manifestations of pulmonary disease that produce these changes in lung function include immune-mediated diffuse alveolar hemorrhage and interstitial lung disease. (Figure 1) shows chest CT of the case.

Arthritis

Musculoskeletal manifestations are a common feature in patients with Copa syndrome, with approximately 95% of the patients with physician-diagnosed arthritis. Age of onset is the early teen years, and polyarticular involvement is common among these patients. The most commonly affected joints are the knees and the interphalangeal joints of the hands. Rheumatoid factor is seen in 43% of reported patients. One patient with chronic polyarthritis was also noted to have elevated level of anti-cyclic citrullinated peptide antibody anitibodies, an autoantibody seen in rheumatoid arthritis that has been correlated with joint destruction [9]. (figure 3) shows arthritis of the case.

Renal Disease

Patients with Copa syndrome also demonstrate increased risk for renal disease. Patients that develop renal disease have an age of onset in their mid to late teen years.

Treatment

Currently, Copa syndrome patients are managed in a similar manner to patients who have other pulmonary hemorrhage and autoimmune syndromes. For pulmonary hemorrhages, most patients are treated with either cyclophosphamide or rituximab during exacerbations. Systemic corticosteroids are also often used to manage the acute phases of exacerbations of disease. Additionally, steroids are useful in other autoimmune components such as arthritis, which has been additionally approached with arthritis-specific disease modifying agents. Remissions in both arthritis and pulmonary disease can often be achieved using these medications. However, due to the progressive nature of Copa syndrome several patients have died during acute exacerbations. Maintenance therapies have usually consisted of either methotrexate or azathioprine with intermittent pulses and gradual tapering oral steroids. Other maintenance therapies may include hydroxychloroquine, etanercept, and IVIG at immuno-modulatory dosages. Unlike other pulmonary hemorrhage syndromes, the optimal duration of therapy is not known.

CONCLUSION:

COPA syndrome should be considered in cases of recurrent fever spikes, polyarthritis, and failure to thrive at an early age. Early diagnosis and treatment can help prevent the progression of interstitial lung disease (ILD) and polyarthritis, and facilitate prompt genetic analysis and family screening.

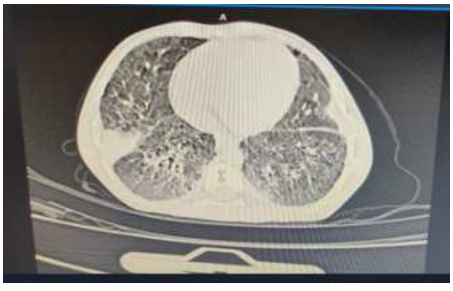

Figure1: CT scan of lung showing interstitial lung disease

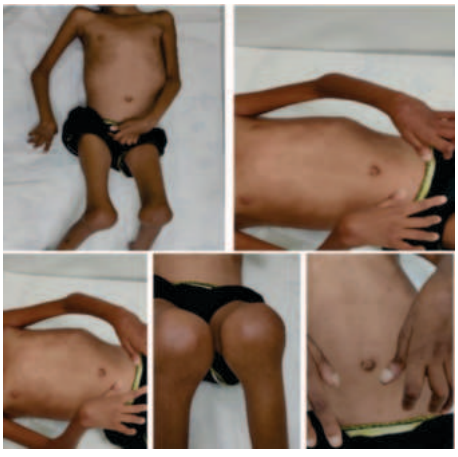

Fig 2: arthritis of multiple joints

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