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INSIGHTS FROM A NOVEL MONOGENIC AUTOIMMUNE DISEASE: OVERVIEW OF A MULTICENTRIC EUROPEAN COHORT OF 27 PATIENTS WITH COPA SYNDROME

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Introduction: COPA syndrome is a recently described monogenic autoimmune disease due to heterozygous mutations in *COPA*. COPA syndrome demonstrates considerable phenotypic overlap with SAVI (STING-associated vasculopathy with onset in infancy) due to gain-of-function mutations in STING.
Objectives: Our aim was to gather a European cohort of COPA patients to better delineate the clinical phenotype of this rare monogenic disorder
Methods: Assessment of clinical, radiological, immunological and therapeutic data from 27 patients (13 families) with molecularly confirmed COPA syndrome.
Results: Twenty-seven individuals with pathogenic COPA mutations were included. Among them, 20 patients presented with at least one clinical manifestation evocative of COPA syndrome (clinical penetrance of 74.1%). Symptomatic patients were female in 13 (65%) cases with a median age at disease onset of 4 years (0-50). All COPA mutations were inherited in an autosomal dominant pattern except for one that occurred *de novo*. Pulmonary involvement was observed in 16 (80%) patients, with interstitial lung disease (ILD) in most cases (n=13, 65%), diffuse alveolar haemorrhage (DAH) in 5 (25%) individuals and the association of ILD and DAH in 3 (15%) patients. Twelve (60%) patients demonstrated joint involvement of variable severity: 4 (20%) individuals experiencing deforming arthritis including one requiring bilateral knee arthroplasty, 6 (30%) patients had polyarticular arthritis and two (10%) patients presented with isolated arthralgias. Renal disease was observed in three (15%) individuals, manifesting as either proliferative glomerulonephritis (n=2) or membranous glomerulonephritis (n=1). Previously undescribed features were noted i.e. cutaneous involvement - acral ulcers, vitiligo and nasal perforation (n=3, 15%), cardiac disease (n=2, 10%), gastrointestinal dysfunction (n=2, 10%), and cytolytic hepatitis (n=1). When tested, 14 (93.9%) patients had positive autoantibodies. When assessed,

immunophenotyping showed a mild T-cell lymphopenia, with an excess of naive T CD8+ cells and a defect of memory T CD8+ cells. All patients explored exhibited elevated IFN alpha protein levels and high IFN signature scores. The IFN signature was mildly positive in half of the clinically asymptomatic individuals assessed. The majority (60%) of patients were treated with corticosteroids and immunosuppressants, ten (50%) received biotherapies and eight (40%) patients are currently under JAK1/2 inhibition.

Conclusion: We report the first European cohort of COPA patients. While confirming the core organ features (lung, joint and kidney) of COPA syndrome, our data expand the phenotype to include cardiac, skin and digestive features, further demonstrating the clinical overlap with SAVI and other type I interferonopathies.In view of current (JAK inhibitors) and potential future targeted therapies, we suggest a requirement to assess IFN pathway status and/or perform sequencing in the case of suggestive features, even in the absence of a familial history.

Patient Consent: Yes, I received consent

Disclosure of Interest: None declared