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Autoinflammatory disorders

Insights from a novel monogenic autoinflammatory disease: overview of a multicentric European cohort of 38 patients with COPA syndrome

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ABSTRACT

Objectives: COPA (coatomer subunit alpha) syndrome is a rare monogenic autoinflammatory disease due to heterozygous mutations in *COPA*. It has phenotypic overlap with STING (Stimulator of interferon genes)-associated vasculopathy with onset in infancy (SAVI), although the spectrum of clinical manifestations is not yet fully defined. Our aim was to better delineate the clinical phenotype of this rare disorder in a European cohort.
Methods: Methods include assessment of clinical, imaging, and immunological data from 46 individuals (29 families) carrying a *COPA* mutation.
Results: Among the 46 individuals carrying a *COPA* mutation, 38 had at least 1 clinical manifestation likely related to their mutant state (clinical penetrance of 83%). Twenty-two (58%)

symptomatic patients were female, with a median age at disease onset of 3 years (range 0-50 years). Pulmonary involvement was observed in 34 patients, with interstitial lung disease in most cases (n = 31) and diffuse alveolar haemorrhage in 11 individuals. Twenty-six patients demonstrated joint involvement, and 7 had documented kidney disease. Previously undescribed features included skin (n = 12), cardiac (n = 8), gastrointestinal (n = 7), and hepatic involvement (n = 5). All but 1 patient tested positive for autoantibodies, and increased interferon signalling was noted in all those tested. Twenty-two patients were treated with Janus kinase inhibitors with promising efficacy.

Conclusions: We report a large European cohort of patients with COPA syndrome. While confirming the core organ features (lung, joint, and kidney) of the disease, our data expand the phenotype to include cardiac, skin, and gastrointestinal features, further demonstrating the clinical overlap with SAVI and other type I interferonopathies.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- COPA syndrome is a rare monogenic type I interferonopathy.
- Known features of the disease are lung, joint, and kidney disease.

WHAT THIS STUDY ADDS

- Expansion of the known phenotype with skin, cardiac, digestive, and hepatic involvement.
- Possibility of clinical nonpenetrance, *de novo* or somatic mutations.
- Morbidity and mortality driven by pulmonary and renal disease.
- Promising efficacy of Janus kinase (JAK) inhibition.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- Sequence the *COPA* gene in the context of a concordant phenotype, even in the absence of a family history of disease.
- Perform a chest computed tomography scan, pulmonary function tests, and a screen for proteinuria in any patient carrying a *COPA* mutation.
- JAK inhibition can be considered as a first-line treatment, and anifrolumab may be a promising therapy to be trialled in COPA syndrome.

INTRODUCTION

COPA syndrome is a monogenic autoinflammatory disease originally described in 2015 due to heterozygous mutations in the gene *COPA*, encoding the coatomer subunit α [1]. In the original paper, 5 families were reported, with symptomatic individuals variably manifesting interstitial lung disease (ILD), inflammatory arthritis, and high autoantibody titres [2]. The authors hypothesised that the disease resulted from defective retrograde transport between the Golgi and endoplasmic reticulum (ER) mediated by the coat protein complex I complex. A major advance in the understanding of COPA syndrome pathogenesis came from the observation of an enhanced expression of interferon (IFN)-stimulated genes (ISGs) in the whole blood of symptomatic individuals, a hallmark of the type I interferonopathies [3]. In addition, clinical overlap was noted with the well-defined type I interferonopathy due to gain-of-function mutations in *STING1* [4], termed STING-associated vasculopathy with onset in infancy (SAVI). STING activation was subsequently shown to be a key driver of the pathogenesis of COPA syndrome [5–8]. Indeed, dominant-negative mutations in COPA prevent STING retrograde transport back to the ER from the Golgi, with associated chronic activation of STING and the induction of the expression of type 1 IFNs and nuclear factor kappa-B-related inflammatory cytokines [5–9].

Since COPA syndrome was first described, approximately 70 cases have been published [2,3,6,10–19]. The core clinical features are lung inflammation with either recurrent alveolar haemorrhage (AH) or ILD [20], joint disease that may mimic juvenile idiopathic arthritis [10–21], and renal involvement [12] with mainly glomerular disease. Given the pivotal role of type I IFN overproduction in the pathogenesis of COPA syndrome, Janus kinase (JAK) inhibition has been proposed as a targeted therapeutic strategy, with apparently promising effects in a number of case reports [13,21].

Here, we aimed to assemble a large European cohort of patients with molecularly confirmed COPA syndrome, thereby providing insights into the clinical and immunological spectrum of the disease, which has been undercharacterised due to the limited number of reported cases.

METHODS

Patients

Patients with genetically confirmed COPA syndrome were included in this retrospective study. Thirteen patients have been previously reported [3,6,10,12,15,21,22]. Patients were recruited from referent rare diseases centres in France, Germany, Italy, Spain, Switzerland, Turkey, Czech Republic, and the United Kingdom. Variants were annotated according to HGVS nomenclature using the MANE select transcript NM_004371.4. All patients had fulfilled the requirements of their local ethics committee for clinical data sharing.

Data collection

Data collected included sex, clinical manifestations at presentation and during follow-up, and age at genetic diagnosis of COPA syndrome. Results of chest computed tomography (CT), pulmonary function tests (PFTs), bronchoalveolar lavage (BAL) fluid analyses, and lung biopsies were recorded. ILD was defined according to CT scan findings, and AH either on CT scan and/or BAL and/or lung biopsy. The presence of honeycombing and/or traction bronchiectasis and/or inter- and intralobular septal thickening radiologically defined pulmonary fibrosis [23]. Biological parameters such as inflammatory markers, autoantibodies, and immunological status were collected, as well as treatment characteristics and the response to therapy.

IFN pathway assessment

Status of IFN biomarkers was determined by studying the expression of ISGs (by qPCR [24] or by NanoString [25]) in

peripheral blood and by measuring IFNα protein in serum using a Simoa ultrasensitive digital enzyme-linked immunosorbent assay [26].

Study approval

The study was approved by the Comité de Protection des Personnes (ID-RCB/EUDRACT: 2014-A01017-40; revalidated in 2022). Written informed consent was obtained for all patients.

Statistics

Data are expressed as median (range) or number (percentages). Analyses were performed using PRISM software (v10, GraphPad Inc.). A *P* value less than .05 was considered significant.

RESULTS

Demographics

Patients from 29 families with genetically confirmed *COPA* mutations were ascertained. Among these, 38 patients demonstrated at least 1 feature suggestive of COPA syndrome (Table 1 and Supplementary Table S1), while 8 individuals were clinically asymptomatic after a full clinical evaluation, pulmonary function testing, lung CT imaging, and assessment for proteinuria. These findings indicate a clinical penetrance of 83% where at least 1 individual in each family had been clinically ascertained. Twenty-two symptomatic patients were female (ratio F:M 1.4:1), while all asymptomatic *COPA* mutation carriers (n = 8), identified through family testing, were female. Among symptomatic patients, the median age at disease onset was 3 (neonatal period-50) years, with 12 patients manifesting disease before the age of 5 years. The median age at molecular diagnosis was 13 (0.3-57) years. At the last follow-up, 34 (89%) symptomatic patients were alive.

Molecular data

All mutations were located in the well-defined mutational hotspot in the WD40 domain of the COPA protein (Fig 1A). Most mutations (61%) identified in symptomatic patients were inherited in a dominant manner from a mutation-positive parent, while 5 occurred *de novo* and 2 patients were somatic mosaic [27], with a variant allele frequency (VAF) of 10% and 29%, respectively. We were unable to test the parents of 8 patients (Table 2). Among symptomatic patients, the p.(Arg233His) (R233H) and p.(Arg281Trp) (R281W) substitutions were the most prevalent, occurring in 13 patients (34%) from 9 pedigrees and 9 patients (24%) from 5 pedigrees, respectively. Additionally, 7 individuals carried a substitution of the amino acid p.(Trp240) (W240) (Table 2). Eight further substitutions were identified in single patients. Half of asymptomatic individuals (n = 4) carried the p.(Arg233His) (R233H) substitution (Table 2). No genotype-phenotype correlation was apparent, and the patients who were somatic mosaic for a *COPA* mutation did not present with a phenotype milder than those seen in the overall cohort (Supplementary Table S1).

Clinical features in symptomatic patients

Clinical characteristics of patients are summarised in Table 1 and detailed in Supplementary Table S1. Features at onset are described in Supplementary Table S1, where recorded. While 10 (26%) symptomatic patients manifest single organ involvement, most individuals experienced at least 2, and up to 6, organs involvement during the course of the disease (Fig 1B). Among patients with single organ involvement, pulmonary disease was

Table 1
Clinical characteristics of affected patients with COPA pathogenic variants at last report.

Demographics	n = 38 patients
Sex ratio (F:M)	1.4:1
Age at onset	3 (0[a]-50)
Age at molecular diagnosis	13 (0.3-57)
Age at last report	15.5 (0.5-58)
Alive/dead at last report	34/4
Organ involvement	
Failure to thrive	14 (37%)
Recurrent fever	9 (24%)
Lung involvement	34 (89%)
ILD	31 (82%)
AH	3 (8%)
ILD and AH	8 (21%)
Fibrosis	14 (37%)
Joint disease	26 (68%)
Polyarthritis	17 (45%)
Arthralgias	6 (16%)
Isolated Boutonniere deformity	2 (5%)
Joint disease without specification	2 (5%)
Skin involvement	12 (32%)
Purpura	2 (6%)
Malar rash	2 (6%)
Acral ulcers/acrosyndrome	3 (8%)
Livedo	1 (3%)
Oral ulcers	1 (3%)
Nasal perforation	1 (3%)
Vitiligo	1 (3%)
Panniculitis	1 (3%)
Psoriasis	1 (3%)
Chilblains	1 (3%)
Not specified skin disease	1 (3%)
Kidney involvement	7 (18%)
ANCA-associated glomerulonephritis	3 (8%)
Not specified kidney insufficiency	2 (5%)
Lupus-like glomerulonephritis	1 (3%)
Membranous glomerulonephritis	1 (3%)
Liver involvement	5 (13%)
Cytolytic hepatitis/secondary to methotrexate	4 (11%)/2 (5%)
Hepatosplenomegaly	1 (3%)
Gut involvement	7 (18%)
Gastro-oesophageal reflux	4 (11%)
Chronic diarrhoea	2 (5%)
Digestive IgA vasculitis	1 (3%)
Stercoral peritonitis	1 (3%)
Cardiac involvement	8 (21%)
Pulmonary hypertension	4 (11%)
Myocarditis	1 (3%)
Mitral insufficiency	1 (3%)
Cardiac hypertrophy	1 (3%)
Not specified cardiac insufficiency	1 (3%)
Ear-nose-throat involvement	1 (3%)
Nasal perforation	1 (3%)
Necrotising sinusitis	1 (3%)
Other features	Retrocerebellar cyst (n = 1), thyroiditis (n = 1), dyslexia (n = 1)

AH, alveolar haemorrhage; ANCA, antineutrophil cytoplasmic antibody; IgA, immunoglobulin A; ILD, interstitial lung disease.
Data are presented as number (percentages) or median (range). Ages are given in years.
[a] Neonatal presentation.

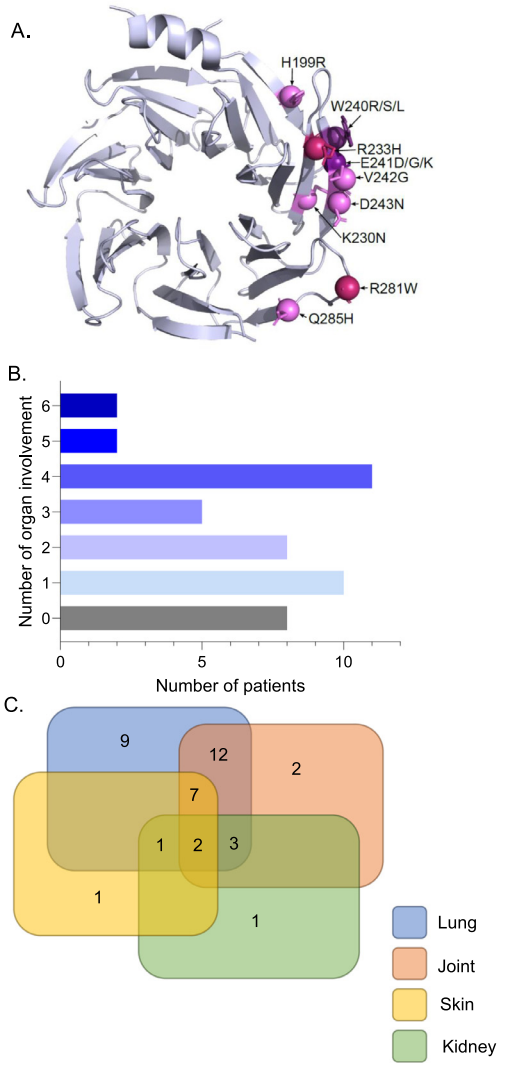

Figure 1. Clinical and molecular spectrum of *COPA* mutations. (A) Location of pathogenic missense mutations within the crystal structure of COPA WD-repeat domain (PDB ID: 6PBG). Substitutions affecting W240 and E241 amino acids are shown in purple. The 2 most frequent substitutions reported in the cohort are represented in darker pink, with other mutations shown in light pink. (B) Number of organs involved per patient in the cohort. (C) Specific and overlapping features present in patients of the cohort, including lung, skin, joint and kidney disease.

Table 2
Clinical penetrance status of the *COPA* mutations identified in the cohort.

Mutation of *COPA*	Symptomatic patients (n = 38)	Asymptomatic carriers (n = 8)
Amino acid substitution		
Het: c.698G>A/p.(Arg233His), R233H	13 (34%)	4 (50%)
Het: c.841C>T/p.(Arg281Trp), R281W	9 (24%)	1 (12%)
Het: c.718T>C/p.(Trp240Arg), W240R	4 (11%)	1 (12%)
Het: c.719G>C/p.(Trp240Ser), W240S	2 (5%)	0
Het: c.719G>T/p.(Trp240Leu), W240L	1 (3%)	0
Het: c.723G>C/p.(Glu241Asp), E241D	2 (5%)	0
Het: c.722A>G/p.(Glu241Gly), E241G	1 (3%)	0
Het: c.721G>A/p.(Glu241Lys), E241K	1 (3%)	0
Het: c.596A>G/p.(His199Arg), H199R	1 (3%)	1 (12%)
Het: c.690G>T/p.(Lys230Asn), K230N	1 (3%)	0
Het: c.725T>G/p.(Val242Gly), V242G	1 (3%)	0
Het: c.727G>A/p.(Asp243Asn), D243N	1 (3%)	1 (12%)
Het: c.855G>C/p.(Gln285His), Q285H	1 (3%)	0
Inheritance		
Autosomal dominant	23 (61%)	
De novo	5 (13%)	
Mosaic[a]	2 (5%)	
Unknown	8 (21%)	

Het, heterozygous.
Data are presented as number (percentages). Amino acid substitutions are annotated according to HGVS. COPA (ENST00000241704.8/NM_004371.4/NP_004362.2).
[a] For F14.P1, the variant allele frequency (VAF) was 29% and 17% in blood and the kidney biopsy, respectively; for F15.P1, the VAF was 10% in blood, 9% in nails, 12% in hair bulbs, and 8% in buccal swab.

the most common (n = 9) (Fig 1C). Regarding general features, 14 (37%) patients manifested failure to thrive, and 9 (24%) recurrent fever.

Lung phenotype

The lung was the most commonly affected organ in the cohort, with 34 (89%) symptomatic patients manifesting pulmonary disease. The majority of patients (n = 21) complained of chronic cough and 14/23 (61%) of dyspnoea, while, at medical examination, 10 individuals had nail clubbing and tachypnoea, respectively. Only 2 patients reported episodes of haemoptysis (Supplementary Table S2). The majority of patients were diagnosed with isolated ILD (n = 23) (Supplementary Table S2 and Fig 2G). Three patients had AH, and 8 patients had both ILD and AH. Radiological (n = 12) and/or histological (n = 5) evidence of fibrosis was observed in 14 patients (41%), including patients aged less than 10 years. Of the 26 patients for whom a chest CT scan was available, ground-glass opacities (n = 22) and cysts (n = 15) were the most frequently recorded anomalies, followed by honeycombing (n = 6), micronodules (n = 5), septal thickening (n = 10), and hilar lymphadenopathy (n = 5) (Fig 2A-C). Where PFTs were performed (n = 19), a restrictive pattern was seen in most patients (n = 13), with other patients displaying either an obstructive (n = 1) or mixed pattern (n = 4). BAL was performed in 16 patients, with fluid analysis revealing AH (n = 6), lymphocytic (n = 8), or neutrophilic alveolitis (n = 2). Lipid-laden macrophages were detected in 2 patients. Ten patients underwent lung biopsy, with follicular hyperplasia (ie, the presence of nonclonal lymphocytic aggregates) observed in all cases (Fig 2E,F). In addition, inflammatory lymphocytic infiltrates were recorded in 6 patients, and signs of fibrosis in 5 individuals. Other histopathological findings included cholesterol pneumonitis, focal organising pneumonitis, cellular nonspecific interstitial pneumonia, fibrosing pleuritis, and alveolar simplification. Six patients required long-term oxygen therapy, while disease in 3 patients necessitated noninvasive ventilation, and 1 individual underwent invasive ventilation with extracorporeal membrane oxygenation during severe AH episodes. Two patients underwent lung transplantation at the age of 23 and 28 years, respectively (See *treatment* section), and 1 other was considered as a candidate for lung transplant at the age of 30 years, but was not eligible due to other clinical disease features (Fig 2G).

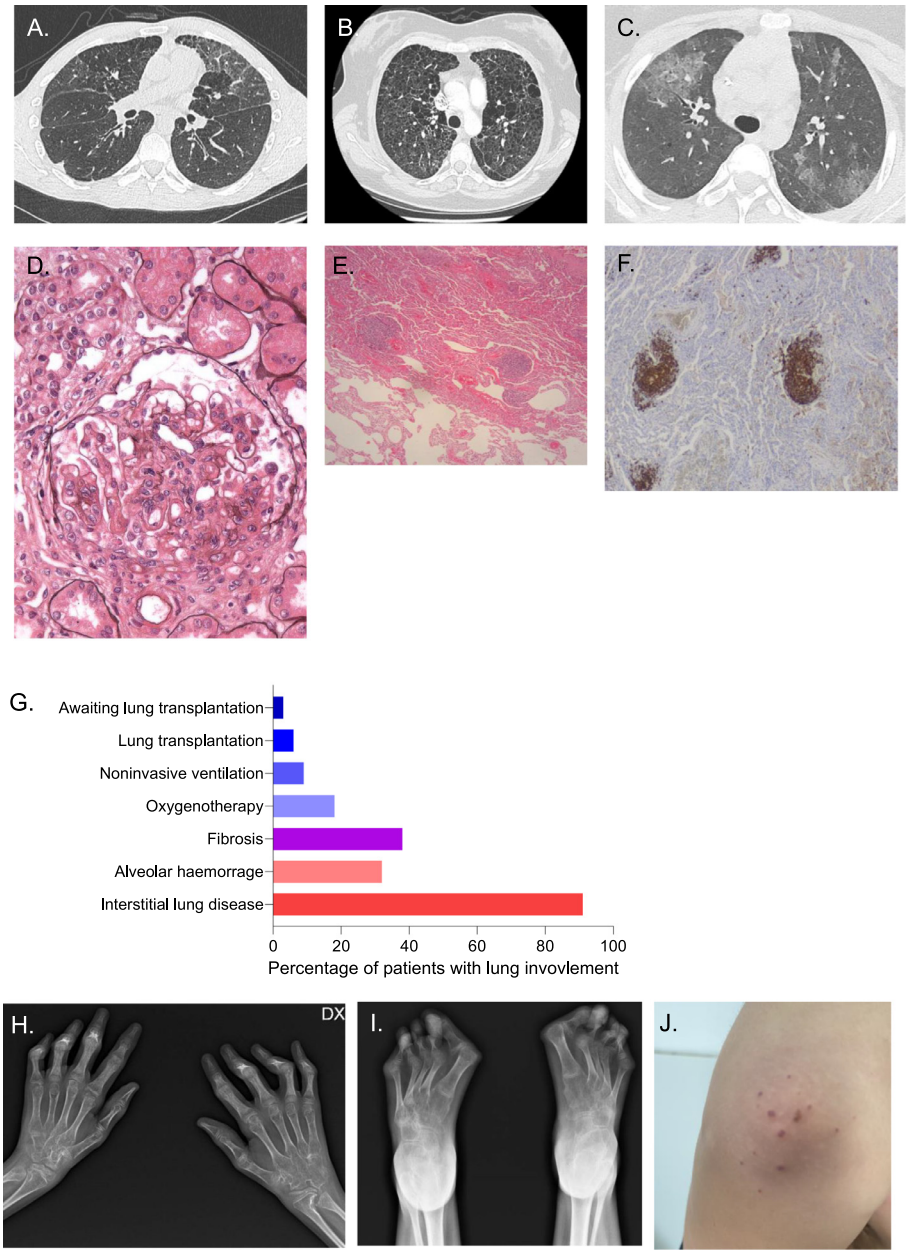

Figure 2. Representative lung imaging and joint disease in COPA syndrome. (A) Chest CT scan of F3.P1 aged 27 years showing ground-glass opacities, cysts and septal thickening. (B) Chest CT scan of F5.P1 aged 24 years demonstrating diffuse cystic lesions. (C) Chest CT scan of F1.P1 aged 12 years with recurrent AH. (D) Kidney biopsy of F2.P4 showing wire-loop thickening of the capillary walls without endocapillary proliferation, presence of a hemi-circumferential cellular crescent and hypertrophy and vacuolation of podocytes. (E) Haematoxylin and eosin (H&E) and Giemsa staining of the lung biopsy of F6.P1 showing subpleural emphysema with local interstitial thickening of the remaining interalveolar septa and lymphoid follicles. (F) CD20 staining of lymphoid follicles showing a predominance of CD20+ B cells. (G) Distribution of pulmonary disease, and requirement for oxygen therapy, noninvasive ventilation or lung transplantation. (H) Hand radiographs of F10.P1 aged 12 years showing diffuse demineralisation, bilateral carpal erosion and ankylosis, erosions with joint pinching of the right 2nd and 5th metacarpophalangeal spaces, and bilateral flaccid deformities of the proximal 2nd to 5th interphalangeal spaces. (I) Foot radiographs of F10.P1 aged 12 years showing diffuse demineralisation and joint misalignment with bilateral major hallux valgus and multifocal metatarsophalangeal dislocations. (J) Purpuric lesions of the elbow of F26.P1 aged 13 years. AH, alveolar haemorrhage; CT, computed tomography.

Joint and muscle involvement

Joint involvement was frequent in the cohort (n = 26 patients, 68%). In particular, 17 (45%) patients presented with polyarthritis, often initially diagnosed as juvenile idiopathic polyarthritis, affecting small, large, and axial joints. Of these, 4 patients suffered from severe disease with joint destruction (Fig 2H,I) and deforming arthritis, 1 of whom required bilateral knee replacement and now uses a wheelchair. Arthralgia without arthritis was seen in 6 patients. Of interest, 2 patients presented Jaccoud-like arthropathy as observed in other type I interferonopathies [28], and Boutonniere deformity of the fingers was documented in 2 further individuals.

Skin disease

Cutaneous manifestations were noted in 12 patients (32%), which were predominantly vascular. Notably, 4 patients presented with acral ulcers, chilblains, or acrosyndrome, 1 with *livedo* and 1 with nasal perforation. Other skin features included purpura (n = 2) (Fig 2J), malar rash (n = 2), panniculitis (n = 1), oral ulcers (n = 1), and psoriasis (n = 1). Skin biopsy of a patient with purpuric lesions of the elbows showed focal leukocytoclastic vasculitis.

Kidney disease

Seven (18%) patients had renal disease. The most common histological pattern was pauci-immune glomerulonephritis associated with antineutrophil cytoplasmic antibody (ANCA) positivity (n = 3 with a specificity for anti-myeloperoxidase (MPO). One patient had lupus-like glomerulonephritis with proliferative lesions associated with focal and segmental glomerulosclerosis and endomembranous deposits of C1q, C3, immunoglobulin M, and immunoglobulin G on immunofluorescence (Fig 2D). Another patient presented a lupus-like membranous glomerulonephritis with a full-house pattern on immunofluorescence and negative antiphospholipase A2 receptor antibodies. In addition, 2 patients had renal insufficiency without further clinical and histological characterisation. Two patients required kidney transplantation (Supplementary Table S3).

Other features

Five (13%) patients presented with hepatic involvement, including 4 individuals with chronic transaminitis, which occurred during methotrexate treatment in 2 cases. Liver biopsy was performed in 1 patient and showed no abnormalities. Seven (18%) patients presented gastrointestinal dysfunction, ie, gastro-oesophageal reflux disease (GERD) (n = 4), chronic diarrhoea (n = 2), gastrointestinal IgA vasculitis (n = 1), and stercoral peritonitis (n = 1). Cardiac involvement was identified in 8 (21%) patients. Pulmonary hypertension was found in 4 (11%) individuals, all presenting with ILD. Right heart catheterisation data were available for 2 patients, showing a precapillary pulmonary hypertension. Three patients were treated with phosphodiesterase 5 inhibitors combined with an endothelin receptor inhibitor in 1 case. The fourth patient affected by pulmonary hypertension had no specific treatment. Further cardiac features included myocarditis, mitral insufficiency, cardiac hypertrophy, and unspecified heart failure (Table 1). Two patients had neurological involvement, ie, asymptomatic retrocerebellar cyst in 1 patient and dyslexia with no brain imaging available in the second one. A patient with ANCA presented with nasal perforation and necrotising sinusitis. Finally, autoimmune thyroiditis was documented in 1 patient.

Asymptomatic carriers were all clinically assessed at molecular diagnosis (between the ages of 24 and 48 years) with normal respiratory examination. Pulmonary investigations (chest CT scan and PFTs) were performed in 3 carriers and were normal.

Immunological features

Inflammatory markers

Inflammatory markers were available in less than half of the cohort. When tested, 6 (55%) patients had a dissociation of their inflammatory markers, ie, an elevated erythrocyte sedimentation rate (ESR) with normal levels of C-reactive protein (CRP) (Supplementary Table S4). Specifically, 9/11 (82%) patients had a high ESR, while 12/19 (63%) and 7/19 (37%) patients had, respectively, normal or only mildly elevated CRP.

Type I IFN assessment

All symptomatic patients evaluated (n = 20) had a positive-type I IFN gene signature (Supplementary Table S4 and S5). Notably, half of the asymptomatic carriers tested also had a positive IFN signature (n = 2), albeit at a lower level than the symptomatic patients (Fig 3A). Serum IFNα protein levels measured by Simoa were high in all symptomatic patients tested (n = 9) (Fig 3B), and the 2 asymptomatic carriers had intermediate levels.

Autoantibodies and immunological features

When tested (n = 31), all but 1 symptomatic patient (97%) had positive autoantibodies (Fig 3C and Supplementary Table S4). Twenty-four (77%) patients had positive antinuclear antibodies, almost all of which were nonspecific except for 5 patients (anti-DNA, n = 1, anti-RNP, n = 2, anticentromere, n = 1, anti-Scl70, n = 1). Fourteen (45%) patients had positive ANCA antibodies (anti-MPO [n = 9], anti-PR3 [n = 2], or both anti-PR3 and anti-MPO [n = 2]). Twelve (39%) patients were positive for rheumatoid factor, and 5 (16%) had positive anticyclic citrullinated peptide (CCP) antibodies (Supplementary Table S4). Six patients presented with hypergammaglobulinaemia.

Lymphocyte immunophenotyping was performed in 7 patients, showing variable modification of lymphocyte subpopulations.

Therapeutics and outcome

Outcome

After a median follow-up period of 48 (6-96) months since the diagnosis of COPA syndrome, 34 patients were alive at last assessment with a median age of 14 (0.5-58) years. Four patients had died. Causes of death included fibrotic progression of ILD and suspected systemic lupus erythematosus without specification at the age of 35 years, respiratory failure at the age of 23 years, and cardiac arrest at home at the age of 31 years, 4 years after lung transplantation. One patient died by suicide.

Treatment

The median number of different immunomodulatory treatments received by each patient was 4 (0-9). More than two-thirds of the patients received at least 2 immunomodulatory drugs (Supplementary Table S3). Seventeen (45%) patients were treated intensively, receiving more than 4 different immune modulators (Fig 3D). Half (55%) of the patients received a disease-modifying antirheumatic drug (DMARD) or a biotherapy (47%) (Fig 3E) during the course of their disease. Twenty-two patients received a JAK inhibitor, most commonly baricitinib (n = 17, 45%) (Supplementary Table S3), with a median age at initiation of 13 (0.5-57) years and a median follow-up under treatment of 24 (0-72) months. Of these 22 patients, 16 (73%) had previously received a DMARD and/or a biotherapy without sufficient efficacy, thereby justifying the introduction of a JAK inhibitor (Supplementary Table S6). For 16 patients, JAK inhibition was clinically assessed to have been associated with disease stabilisation or improvement: joint and lung disease improved in 7 patients each, and stabilised in 1 and 6 patients respectively. However, despite treatment, disease progression was noted in 5 patients, including uncontrolled joint disease in 3 cases and lung disease progression in 2 patients. One additional patient had just started treatment. No serious infectious adverse events were noted except in 1 patient on high-dose baricitinib who presented with meningococcal pneumonitis. Two patients received a lung transplantation, and 2 patients received a kidney transplantation. The first patient who underwent lung transplantation had a favourable pulmonary outcome, but subsequently died of cardiac failure 4 years post transplantation. The other one is stable 6 months post transplantation. Kidney function of the 2 patients who underwent kidney transplantation is stable 2 years post transplantation.

DISCUSSION

Previous case descriptions of COPA syndrome provided initial insights into the phenotypic pleiotropy of this rare autosomal dominant disorder [2,5–7,10,12,17,19,29]. The European cohort described here, comprising 38 symptomatic patients, confirms the known core features of COPA syndrome, ie, lung inflammation, arthritis, and kidney disease [2], and further expands the disease spectrum.

In our cohort, most cases manifest early in life, although some cases demonstrated a later onset. Almost 90% of patients manifested pulmonary involvement. Some key features can be delineated to help clinicians diagnose COPA syndrome-related lung disease, which is of particular concern given the high associated morbidity due to progression to fibrosis and end-stage respiratory failure. Clinically, almost half of the patients had nail clubbing, as reported in other cases [14,17], which should be looked for in patients with unexplained autoinflammatory disease. However, lung disease can be strictly asymptomatic;

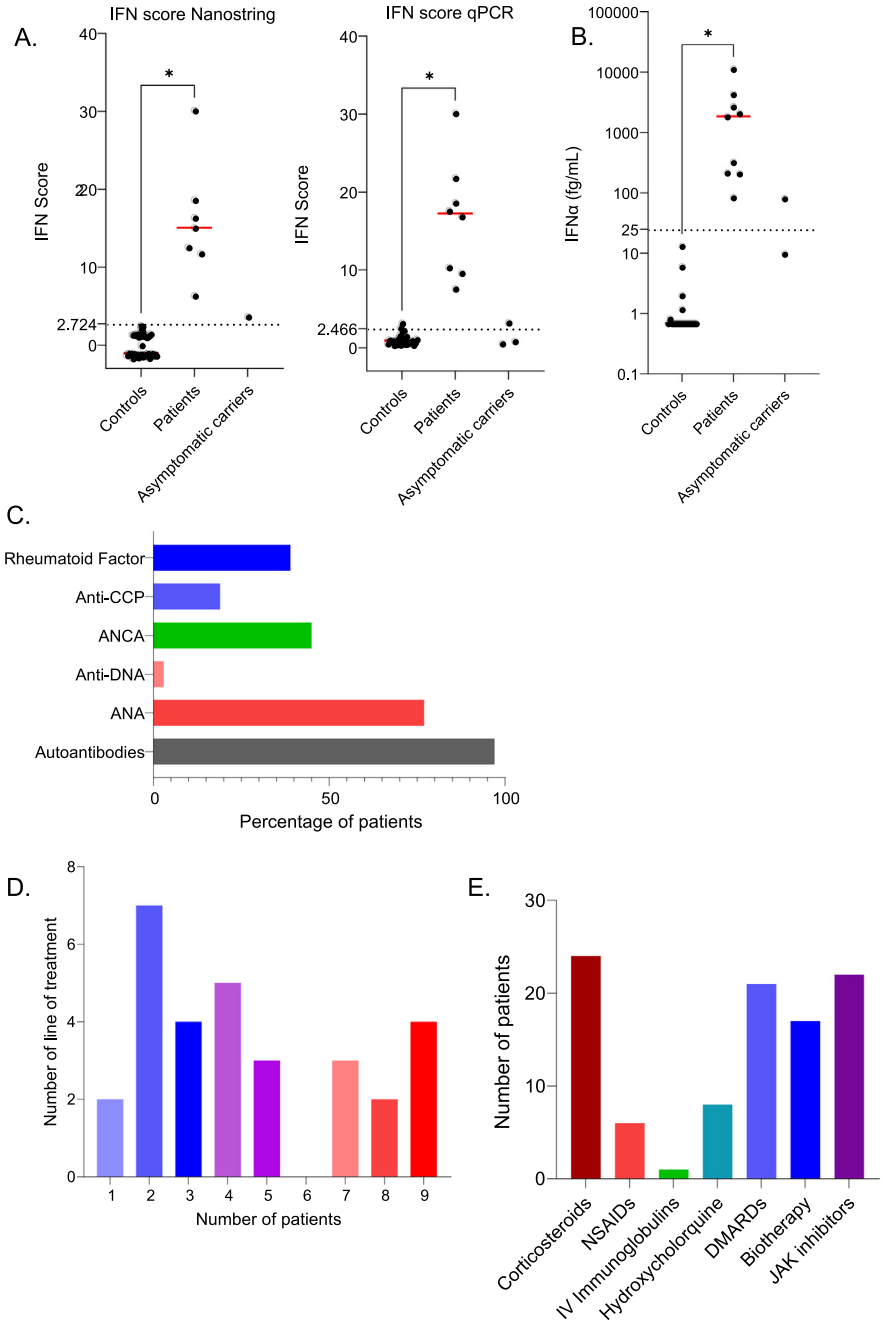

Figure 3. Immunological features and treatment exposures in symptomatic patients with COPA syndrome ascertained in this study. (A) Interferon-stimulated gene (ISG) expression measured in controls, patients and asymptomatic carriers, using either a 24 (left) or 6 (right) ISG panel (measured on a NanoString platform or using RT-qPCR, respectively) to calculate an IFN score. (B) Concentrations of IFNα protein assessed by ultrasensitive digital ELISA (Simoa) in serum from healthy controls (n = 20), patients and asymptomatic carriers. (C) Autoantibodies observed in the cohort: rheumatoid factor (RF), anticyclic citrullinated protein (CCP) antibodies, antineutrophil cytoplasm antibodies (ANCAs), antidouble-stranded DNA (anti-DNA), antinuclear antibodies (ANAs). (D) Number of lines of treatment received by each patient. (E) Number of patients receiving corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), intravenous (IV) immunoglobulins, hydroxychloroquine, disease-modifying antirheumatic drugs (DMARDs), biotherapy or JAK inhibitors. ****$P < .0001$ using Mann-Whitney U test. ELISA, enzyme-linked immunosorbent assay; IFN, interferon; JAK, Janus kinase; RT-qPCR, reverse transcription quantitative polymerase chain reaction.

therefore, a chest CT scan and PFTs should be performed. As previously described [14], AH can be insidious—with only 2 patients in our cohort presenting with episodes of obvious haemoptysis, and must be looked for on chest imaging (X-ray or CT scan) or in BAL. Regarding lung CT imaging, the most common pathological pattern was of ground-glass opacities. In more than half of the patients, a particular pattern consisting of diffuse cystic lesions was observed. Such cystic lung lesions have also been reported in other genetic type I interferonopathies, most particularly SAVI [30,31]. These cystic lesions might be the radiological consequence of the follicular bronchiolitis or lymphoid follicles found in all patients on biopsy [32]. The lung CT abnormalities seen in our cohort were consistent with other case series [33], except for 'crazy paving', which we did not record. BAL analysis was not specific, with the observation of diverse histopathological patterns.

The second major organ involved was the musculoskeletal system, as previously reported [2,11,13,21], with a wide spectrum and severity of manifestations ranging from arthralgia to destructive polyarticular arthritis regardless of anti-CCP status. Although considered as a core feature of COPA syndrome [2,34], renal disease was recorded in less than a quarter of our cohort. The majority of patients presented with ANCA-like pauci-immune glomerulonephritis, highlighting the fact that COPA syndrome may mimic ANCA vasculitis, as also illustrated by the finding of nasal perforation and necrotising sinusitis in 1 patient. Given the high associated morbidity, renal disease should be searched for in all individuals carrying a pathogenic COPA mutation, with 2 patients in our cohort requiring kidney transplantation. Renal disease can be isolated, underscoring the need to enquire about family history and assess type I IFN signalling in patients with unexplained glomerulopathy [34].

We observed several clinical features not commonly or previously reported in COPA syndrome. Notably, almost one-third of our cohort manifests skin disease, reminiscent in some cases of the skin vasculopathy seen in SAVI and other type I interferonopathies [35]. Other rare organ involvement included the hepatic, gastrointestinal, and cardiac systems. While hepatic

disease has only been previously reported once [29], we recorded 5 patients with hepatic manifestations in our cohort, highlighting the possibility of an underestimation of hepatic disease in COPA syndrome. Of note, 2 patients developed transaminitis after methotrexate, raising concerns about the use of hepatotoxic drugs in the context of COPA syndrome and other type I interferonopathies, where severe liver damage has been observed in a few case reports [36,37]. Studies of metabolic dysfunction-associated steatotic liver disease and viral hepatitis suggest a deleterious effect of STING signalling on hepatocytes [38] that could account for a possible increased risk of hepatoxicity in monogenic diseases driven by STING activation. Twenty per cent of patients experienced gastrointestinal symptoms, primarily GERD, for which the direct involvement of COPA dysfunction is not clear. Since GERD can worsen lung inflammation and has been reported in SAVI [30], it seems sensible to track and treat GERD in patients with COPA [39]. Finally, pulmonary hypertension has never been described in the context of COPA syndrome. However, 4 patients in our cohort had World Health Organization group 3 pulmonary hypertension. A direct effect of the type I IFN pathway in the development of pulmonary hypertension is also possible, as some evidence has been reported linking type I IFN and STING signalling to pulmonary hypertension [40,41], and pulmonary hypertension has been recorded in patients having type I interferonopathies without lung disease [42]. This study also highlighted another clinical overlap with SAVI: the lack of neurological involvement, which is a core feature of Aicardi-Goutières syndrome and other type I interferonopathies. The diversity of type I interferonopathy phenotypes is not fully understood but is likely to arise from differences in cellular or tissue sources of IFN. The number of patients with COPA syndrome reported in the literature is still small, and it is likely that the full extent of the associated clinical spectrum is yet to be defined. For these reasons, we have been comprehensive in our description of the clinical features observed in the patients described here. At the same time, we recognise that features such as vitiligo and GERD are seen at relatively high frequency in the general population, so that establishing a definitive relationship to COPA dysfunction is not possible at this time. Overall, the phenotypic spectrum of COPA syndrome is strikingly diverse and deserves careful clinical assessment, with some patients having isolated organ manifestation and others multiorgan involvement. As some patients develop novel organ involvement with age, physicians should continue to monitor patients over time.

COPA syndrome is an autosomal dominant disease due to heterozygous mutations inherited from a mutation-positive parent in most cases. In our cohort, the mutation occurred *de novo* in 4 patients. In addition, 2 patients presented with mosaicism, which has not been previously reported in COPA syndrome, but has been seen in other type I interferonopathies [43]. This observation indicates the requirement for a reduction of the VAF detection threshold in molecular diagnosis. In addition to the possibility of *de novo* mutation or mosaicism, another challenge in the diagnosis of COPA syndrome is the high degree of clinical nonpenetrance. Nearly 19% of the individuals in our cohort carried a pathogenic COPA mutation in the absence of clinical signs, a finding consistent with the literature [2]. All asymptomatic carriers in our cohort were women. However, several male asymptomatic carriers have been described by other teams [2]. Interestingly, half of the asymptomatic carriers presented a mildly elevated IFN score, suggesting that other factors—such as additional genetic, environmental, epigenetic influences [44] or monoallelic expression [45]—might play a protective or aggravating role in determining phenotypic status. When assessing the pathogenic prediction scores of *COPA* variants *in silico*, the predicted scores were high for all mutations except for the Q285H variant [10]. Of possible note, the Q285H variant was seen in a patient with a relatively mild phenotype, ie, isolated joint disease. Except for this example, no genotype-phenotype correlation has been suggested or reported in COPA syndrome.

All of the mutations in our cohort were located in the same hotspot in the N-terminal part of COPA protein, encompassing exons 7, 8, 9, and 10. The location of these *COPA* mutations is directly linked to the pathogenesis of COPA syndrome as they affect the WD40 domain, which plays a key role in the recognition of STING for its retrograde transport. Recently, mutations in the C-terminal part of *COPA* have been published as causative of COPA syndrome [46]. These mutations do not seem to directly affect STING signalling and might be considered as causing a different disease with a more severe inflammatory phenotype. The precise pathogenesis of COPA syndrome is incompletely understood, as some features may be independent of IFN signalling [47], given that STING can mediate non-IFN-related effects [47]. Moreover, *COPA* mutations may affect protein trafficking beyond STING [1], having been shown to (also) cause ER stress and upregulated Th17 immunity [2]. The use of novel therapies, specifically targeting type I IFN signalling, such as the monoclonal anti-IFNAR1 antibody anifrolumab [48], will help in discriminating the IFN-dependent and independent pathogenesis of COPA syndrome.

Patients with symptomatic COPA experience a high disease burden, with the majority receiving multiple lines of immunosuppressive treatment. Although our study was not designed to assess the response to treatment, JAK inhibition targeting the type I IFN receptor downstream signalling was the most commonly used treatment approach, and was assessed to effectively control at least some aspect of the disease in more than two-thirds of the cases—as previously reported by us and others [13,18,21]. Except for 1 patient who developed meningococcal pneumonia, no other serious adverse events were recorded in the cohort. However, as severe infectious events have been reported with JAK inhibition, all patients should be screened for VZV (varicella-zoster virus) status and offered zoster vaccination when indicated, and BK, EBV (Esptein-Barr virus), and CMV (cytomegalovirus) viraemia should be monitored frequently during follow-up. Unfortunately, in some patients disease still progressed despite JAK inhibitor treatment, and end-stage organ failure occurred in several patients—as manifest by the requirement for lung and kidney transplantation in several patients in our cohort and in the literature [16,49]. Of note, lung transplantation in the context of COPA syndrome or SAVI is challenging, with poor outcomes in most patients [50,51]. Specifically, several patients experienced acute allograft dysfunction, with or without high levels of interleukin-6, highlighting the need to improve the immunosuppressant strategy in the context of constitutive activation of immune cells [16,49,50]. Understanding the specific and relative role of immune cells (monocytes, lymphocytes) and lung resident cells (alveolar epithelial cells, lung endothelial cells) in the pathogenesis of the lung inflammation seen in COPA syndrome and SAVI is crucial to optimise patient care [20].

Here, we describe, to our knowledge, the largest cohort of patients with COPA yet reported. While confirming the known core phenotype of COPA syndrome, we have broadened the clinical spectrum of this severe type I interferonopathy to include other features. Pulmonary and renal disease drive morbidity and mortality in COPA syndrome and should be a focus to prevent

progression to irreversible organ damage. The presence of *de novo* and mosaic mutations, in addition to clinical nonpenetrance, should prompt clinicians to assess type I IFN signalling status and/or sequence *COPA* in the presence of a concordant phenotype, even in the absence of a family history. JAK inhibition is currently the most common therapeutic strategy used. In the future, the availability of novel treatments that specifically target the type I IFN pathway, particularly anifrolumab [48], will be worth considering in the treatment of COPA syndrome. In the meanwhile, disease pathogenesis remains incompletely understood, particularly the mechanism of lung inflammation [20], an understanding of which will require further functional and therapeutic studies to improve patient management.

Competing interests

All authors declare they have no competing interests.

Patient consent for publication: Written consent was obtained for pictures appearing in the manuscript.

Ethics approval: The study was approved by the Comité de Protection des Personnes (ID-RCB/EUDRACT:2014-A01017-40; revalidated in 2022). Written informed consent was obtanied for all patients.

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CRediT authorship contribution statement

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Supplementary materials

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