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Case-based Review

Baricitinib in therapy of COPA syndrome in a 15-year-old girl

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Abstract

COPA syndrome is a newly discovered hereditary immunodeficiency affecting the lung, kidneys, and joints. The mutated gene encodes the α subunit of the coatomer complex I, a protein transporter from the Golgi back to the endoplasmic reticulum. The impaired return of proteins leads to intracellular stress. The syndrome is an autoimmune and autoinflammatory disease that can be grouped among the interferonopathies. The knowledge about COPA syndrome and its treatment is still limited. In this paper, we describe an additional patient, a 15-year-old girl with rheumatoid factor-positive polyarthritis and rheumatoid nodules since the age of 2, who developed interstitial lung disease. The detected mutation c.698G>A was causing the disease. The patient presented with symmetric polyarthritis on wrists, fingers, and hip and ankle joints, with significant functional impairment, and high disease activity. Laboratory parameters demonstrated chronic inflammation, hypergammaglobulinemia, high titre ANA (antinuclear antibodies) and CCP (anti-citrullinated protein) antibodies, and rheumatoid factors. Therapies with various DMARDs (Disease Modifying Anti-Rheumatic Drugs) and biologicals failed. Upon baricitinib application, the clinical activity decreased dramatically with disappearance of joint pain and morning stiffness and significant decrease of joint swelling. A low disease activity was reached after 12 months, with complete disappearance of rheumatoid nodules. In contrast to IL-1 (interleukin-1), IL-6, and TNF (tumor necrosis factor) inhibitors, baricitinib was very successful, probably because baricitinib acts as a JAK-1/2 (janus kinase-1/2) inhibitor in the IFNα/β (inteferone α/β) pathway. A relatively higher dose in children is necessary. COPA syndrome represents a novel disorder of intracellular transport. Reviewing published literature on COPA syndrome, in addition to our patient, there were 31 cases further described.

Keywords: Systemic lupus erythematosus, belimumab, biological treatments, serositis, pleuropericarditis

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Introduction

In 2015, Watkin et al. (1) first described the occurrence of inflammatory arthritis, interstitial lung disease, renal disease, and high-titer autoantibodies in five different families. Causative heterozygous missense mutations could be found in the COPA gene coding for the coatomer complex I, subunit alpha (COPα), which is why the syndrome is now known as COPA syndrome. The inheritance pattern is autosomal dominant with variable penetrance. Patient symptoms are caused by impairment of retrograde transport of protein vesicles from the Golgi complex to endoplasmatic reticulum (ER), leading to increased mRNA protein translation and inducing ER stress, followed by immune dysregulation. While the expression has been found ubiquitously in all cell types, only joint, renal, and pulmonary tissues seem to be affected and therefore presenting pathogenic changes described above. The onset of symptoms usually takes place before the age of 5 (1). To this day, an optimal treatment has not been defined.

Case Presentation

Here we describe a female patient who suffered from polyarthritis beginning at an age of 2 years. She had no family history of rheumatologic diseases. Because of gastric reflux, she underwent hemifundoplication and fundoplication in 2010 and 2013, respectively. Over the course of time, pulmonic impairment began.

Initially, a rheumatoid factor (RF) -positive juvenile idiopathic arthritis (JIA) was suspected, although at the age of 2, the occurrence of RF, CCP (anti-citrullinated protein) antibodies, and rheumatoid nodules is very rare.

In 2016, the lung function testing showed restrictive and obstructive signs due to interstitial lung disease (VC 48.1%, FEV1 54.2%). Genetic testing for cystic fibrosis and primary ciliary dyskinesia was normal. Not before 2017, newly discovered COPA syndrome was confirmed using the Sanger sequencing of coding exons 8 and 9 of the COPA gene. A heterozygous missense mutation was found on the position c.698G>A, p. Arg233His, which has been previously described in 15 patients from four unrelated families (1-3).

Laboratory results from June 2017 detected elevated CD3/CD4 (cluster of differentiation 3/4) helper cells with otherwise normal lymphocyte subpopulations, persisting a high ANA (antinuclear antibodies) titer (1:640), high-titer RF (591 IU/mL), and elevated anti-citrullinated protein antibodies (>340 IU/mL).

Thus far, treatment with corticosteroids, methotrexate, golimumab, etanercept, adalimumab, abatacept, tocilizumab, rituximab, leflunomide, and azithromycin had been tried. Resilience improved with systemic corticosteroids. A combination of etanercept and methotrexate induced remission for years but could not be continued due to negative effects of methotrexate on the lungs. Monotherapy with etanercept was insufficient.

Therefore, in July 2017, treatment with baricitinib (initially 4 mg once daily) was started in addition to the pre-existing treatment with methotrexate 10 mg once weekly, folic acid 5 mg once weekly, vitamin D 1000 IE daily, and growth hormone 1.2 mg daily. At that time, the patient showed active polyarthritis with painful swelling of the right knee, both wrists, both ankle joints, right forefoot, and multiple finger joints affecting MCPs and PIPS, pain on motion of both hips as well as multiple rheumatoid nodules. The clinical juvenile arthritis disease activity score was 20 (cJADAS; range, 0-30), and the childhood health assessment questionnaire disability index was 1.25 (CHAQ-DI; range, 0-3) (Figure 1).

Since previous reports of interferonopathies like CANDLE (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature) or SAVI (STING-associated vasculopathy with onset in infancy) treated with baricitinib showed that children needed a significantly higher dose compared to adults (4) and initial daily dosage for children weighing between 20-40 kg should be 6 mg, we decided to increase baricitinib to 6 mg daily in divided doses (4 mg, 0 mg, and 2 mg) (Figure 1). At that time, total amounts of immunoglobulin A, M, and G were elevated (IgG 18.3 g/l, IgA 2.7 g/l, and IgM 2.8g/l). Blood sedimentation rate was significantly increased (52 mm/h) with a normal level of CRP (C-reactive protein; 3.86 mg/l; 0-5 mg/l), representing chronic inflammation.

Main Points

- COPA syndrome is a novel autoimmune and inflammatory disease.
- Patients with uncontrolled symptoms of JIA and pulmonal impairment might be suffering from COPA syndrome.
- Baricitinib seems to be a successful treatment for patients with COPA syndrome.

Only 6 weeks after increasing dosage, joint swelling, pain, and morning stiffness decreased, rheumatoid nodules vanished, and the number of active joints was reduced to 6 from 20. After over a year of treatment, the clinical score cJADAS decreased to 4 (0-30) and CHAQ to 0 (0-3). Parent's and physician's visual analog scale (VAS) dropped from 5 to 0/1 (Figure 1). The height increased by 4.5 cm in 12 months. The lung function was stabilized and still showed signs of restriction, but with a slight improvement (vital capacity 50%).

Overall, the treatment with baricitinib seemed to be very successful. Considering great clinical improvement, a similar decrease of chronic inflammation in blood results was expected. Interestingly, the blood sedimentation rate after 6 weeks of treatment with an increased dosage was still at 85 mm/h, and the amounts of immunoglobulin A, M, and G remained elevated. The CRP amount again showed a normal result. This chronic inflammation did not change at first in the following check-ups. However, the last blood test after over a year of treatment showed normal results for IgG, with IgA and IgM still being slightly increased. The blood sedimentation rate decreased to 32 mm/h, while the RF titre and anti-CCP-antibody titres remained highly elevated. Written informed consent was obtained from the parents of the patient.

Literature Review

COPA syndrome is a novel disease first described in 2015 (1). To this date, a total of 31 patients have been reported, 21 initially described by Watkin et al. (1), 4 by Taveira-DaSilva et al. (3), 3 by Jensson et al. (5), and 1 each by Brennan et al. (6), Noorelahi et al. (7), and Vol-

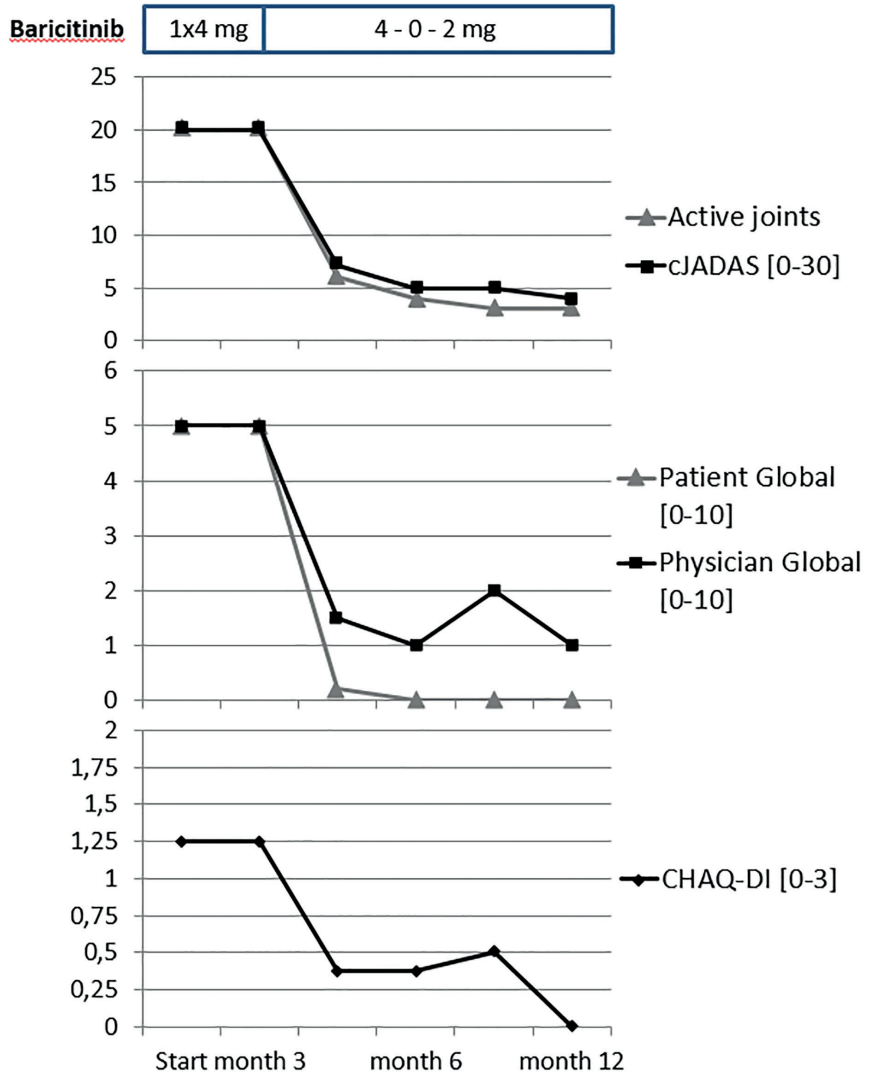

Figure 1. Course of disease activity parameters upon treatment with baricitinib. A marked decrease of the number of active joints (range, 0-71), cJADAS (range, 0-30), physician's global assessment of disease activity, measured on a 0-10 VAS, parent global assessment of well-being, measured on a 0-10 VAS where 0 equals very well and 10 equals very poor, and CHAQ-DI (range 0-3) was observed after increasing the dosage to 6 mg daily 3 months after starting the treatment with baricitinib.

pi et al. (2) (Table 1). At the time of writing, a literature review of PubMed revealed 7 publications about newly defined COPA syndrome for the searched term "COPA syndrome," and 1 additional case report was published as an oral abstract (6).

Watking et al. (1) and Vece et al. (8) both described the same initial cohort consisting of 21 patients with COPA syndrome. Five different families could be found whose members mostly presented with respiratory symptoms. Systemic steroids, cyclophosphamide and rituximab were used for acute exacerbations, and the maintenance therapy included methotrexate, azathioprine, hydroxychloroquine, etanercept, and IVIG (intravenous immunoglobulin). Details on the efficacy of agents used for therapy has not been described, but the response to immunosuppression is stated as 100 %.

Taveira-DaSilva et al. (3) described a kindred consisting of 4 affected patients in 3 generations. The onset of symptoms progressed in successive generations. Apart from typical symptoms affecting lungs (follicular bronchitis, interstitial lung disease) and arthritis, they report atypical findings like renal clear cell carcinoma, nephrolithiasis, cysts in the liver and kidney, neuromyelitis optica, and carcinoid tumor. Data about the treatment and its efficacy were not shown.

Jensson et al. (5) report a family with 3 affected patients in 2 generations. Severe restrictive lung disease led to lung transplantation in 2 cases. No renal impairment could be observed. Patients received treatment with steroids, NSAIDs (nonsteroidal anti-inflammatory drugs), azathioprine, mycophenolat mofetil, methotrexate, azithromycin, salazopyrin, TNF inhibitors, and immunoglobulins. Details on efficacy were not described.

A 4-year-old girl was presented by Brennan et al. (6) with arthritis, restrictive lung disease, and gastro-esophageal reflux. She also developed macrophage activation syndrome. Treatment with steroids and methotrexate initially led to remission of arthritis but could not prevent progress of pulmonary impairment. At the time of writing, her medication included mycophenolate mofetil, hydroxychloroquine, prednisolone, and prophylactic antibiotics. There is no published information about the efficacy.

Noorelahi et al. (7) report a 12-year-old boy with COPA syndrome. A severe restrictive lung defect was to the fore, but polyarticluar arthritis followed subsequently. Disease activation could be managed well on methotrexate, adalimumab, and naproxen.

Another female patient with COPA syndrome was described by Volpi et al. (2). She first presented with arthritis and developed interstitial lung disease over time. Disease activity could be controlled with steroids (high dose intravenously and orally), but the combination of methotrexate and abatacept was not effective. After the diagnosis of COPA syndrome, the treatment with mycophenolate mofetil, hydroxychloroquine, and steroids was able to control the disease progression.

Including our patient, the majority of patients was under the age of 5 at the time of presentation (66%) and female (63%). In contrast to our patient, only 34% initially presented with joint pain, whereas tachypnea, cough, or hemoptysis occurred in 63%. Over time, both arthritis and interstitial lung disease developed in 88% and 97%, respectively, of cases described. Interestingly, similar to our patient, Brennan et al. (6) reported a patient who also developed gastro-oesophageal reflux with the need of surgical treatment. Our patient also underwent hemifundoplication and fundoplication in 2010 and 2013, respectively. No other patient in literature with COPA syndrome has been reported to have significant gastric reflux, to the best of our knowledge.

So far, for treatment, immunosuppression is central and has been shown to be effective as steroids induce remission of the arthritis (1, 2, 9). Corticosteroids, mycophenolate mofetil, and methotrexate are the most common second agents. Others, such as hydroxochloroquine, azathioprine, rituximab, and adalimumab have been tried as well. Vece et al. (8) reported a sufficient response using several agents: non-biological disease modifying drugs such as azathioprine, methotrexate, cyclophosphamide, hydroxychloroquine, and biologics such

Table 1. Clinical and demographic characteristics of all cases with COPA syndrome that were published.

Reference		1, 10	7	2	6	5	3	Our Patient	Total	%
Patients in total		21	1	1	1	3	4	1	32	100
Age at presentation <5 yrs		16	0	1	1	1	1	1	21	66
Sex	female	13	0	1	1	2	2	1	20	63
	male	8	1	0	0	1	2	0	12	38
Initial symptoms	joint pain	5	0	1	1	3	0	1	11	34
	tachypnea, cough, hemoptysis	14	1	0	0	2	3	0	20	63
Arthritis		20	1	1	1	3	1	1	28	88
Pulmonary hemorrhage or interstitial lung disease		21	1	1	1	3	3	1	31	97
Autoantibodies	ANA	14	1	1	1	3	0	1	21	66
	ANCA	15	0	0	n.k.	0	n.k.	n.k.	15	58
	RF	9	1	1	n.k.	3	2	1	17	55
	CCP antibodies	n.k.	1	n.k.	n.k.	2	n.k.	1	4	80
Response to immunosuppression		21	1	partial	initially	n.k.	n.k.	1	23	100

ANA: antinuclear antibodies; ANCA: anti-neutrophil cytoplasmic antibody; CCP: anti-citrullinated protein; n.k.: not known; RF: rheumatoid factor

as etanercept and rituximab. Whereas Volpi et al. (2) reported response to corticosteroids, hydroxychloroquine, and mycophenolate mofetil, the efficacy of the same treatment combination in the patient described by Brennan et al. (6) is unknown but likely to be disease controlling(. The combination of methotrexate and abatacept was described as ineffective by Volpi et al. (2). For seven remaining patients, the data of response to treatment are not available in literature (3, 5). Thus, there is a wide variety for immunosuppressive agents used for treatment, and most of the patients are treated with more than two agents (2, 5, 6, 7).

Suggesting a mixed-pattern disorder with features of autoimmunity and autoinflammation, Volpi et al. (2) found Type 1 interferon to be possibly involved in the disease pathogenesis and proposed effective treatment with Janus kinase inhibitors or anti-interferon monoclonal antibodies. As a selective Janus kinase inhibitor of JAK-1 and JAK-2, treatment with baricitinib is a promising approach since its successful use in interferonopathies such as CANDLE and SAVI (10). Especially since patients with SAVI show clinical similarities to COPA patients (8, 11), Volpi et al. (2) investigated COPA patients for a Type 1 interferon signature showing strong upregulation. To this date, to the best of our knowledge, the treatment with baricitinib has only been tried in our patient suffering from COPA syndrome.

It should be noted that children with interferonopathies like CANDLE or SAVI need a significantly higher dose of baricitinib compared to adults, which must be given in divided doses (4). It stands to reason that this applies to COPA syndrome as well due to its clinical and serological similarities. Results of our presented patient underline this consideration. According to Kim et al. (4), baricitinib could be increased further to 8 mg daily in our patient weighing between 20 and 40 kg. At present, such an increase for our patient is not necessary but could be required in future. For predominantly renal elimination of baricitinib, regular safety analyses are required due to possible kidney involvement, especially in patients with COPA syndrome, which additionally impairs the renal activity. The presented patient so far shows no signs of the renal disorder.

A mixed pattern disorder with the involvement of expansion of Th17 lymphocytes, as well as the activation of Type 1 interferon pathway could also lead to another target point in therapy (2). The blockage of IL-12/23 using ustekinumab is a conceivable option. Nevertheless, Tsui et al. (9) do not yet recommend therapies targeting Th17 cells as immunopathogenesis remains not fully understood, and findings need to be replicated.

Conclusion

To the best of our knowledge, this is the first report of baricitinib treatment in a pediatric patient with COPA syndrome. The patient was first diagnosed with JIA. The occurrence of interstitial lung disease, however, led to a more distinct diagnostic work up. Diagnosis of COPA syndrome was confirmed genetically with a typical mutation found, which might be an explanation for the failure of several therapeutic attempts. One should bear in mind that patients with similar symptoms and therapy resistance might be suffering from undiagnosed COPA syndrome. So far, only a limited number of patients have been described in literature. This is likely due to just recent knowledge of this syndrome and its genetic pathogenesis. Vece et al. (8) state that COPA syndrome may not be very rare as they identified patients rather quickly. Tsui et al. (9) recommend to consider genetic testing if at least two extrapulmonary features (disease onset <12 years, family history of disease, positive results for ANA, ANCA (anti-neutrophil cytoplasmic antibody) or RF, arthritis) and one pulmonary feature (follicular bronchiolitis, cysts, diffuse alveolar hemorrhage) are present.

In summary, we describe successful treatment with baricitinib of a patient suffering from COPA syndrome. As an inhibitor of JAK-1 and JAK-2, baricitinib seems to have a positive influence on the Type 1 interferon pathway. Other target points, such as blockage of IL-12/23, could be possible in future, but further research in this field will be necessary to optimize the treatment of affected patients.

Informed Consent: Written informed consent was obtained from the parents of the patient we described here.

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