

Anti-Jo-1 antisynthetase syndrome

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ABSTRACT

Objective: Given a lack of population-based studies, we report an epidemiological-clinic study of anti-Jo-1 antisynthetase syndrome (ASS). **Patients and Methods:** To study a retrospective cohort of a single-center from 1980 to 2010. Clinical-laboratory and demographic data were obtained from medical files. All patients fulfilled the Bohan and Peter criteria (1975) and presented anti-Jo-1, articular, muscle and lung involvement. Eighteen patients with anti-Jo-1 ASS were analyzed. **Results:** The mean age at disease onset was 39.9 ± 15.7 years and average disease duration was 9.7 ± 7.0 years. All subjects were white, and 94.4% were female. Constitutional symptoms occurred in 50% of cases. There was cutaneous and gastrointestinal tract involvement in 66.6% and 55.6% of cases, respectively. No cases manifested neurologic or cardiac involvement. Half of the patients showed incipient pneumopathy, ground-glass opacities and basal pulmonary fibrosis. There was one case of tuberculosis, three of herpes zoster and one of non-Hodgkin lymphoma. One death occurred due to sepsis shock (hospital bronchopneumonia). All patients received prednisone (1mg/kg/day) and 12 (66.7%) participants received methyl prednisolone pulse therapy (1g/day, 3 days). Various immunosuppressants were used as corticosteroid tapers, depending on tolerance, side effects and/or refractoriness. Although disease relapse (clinical and/or laboratory) occurred in 87.5% of cases, 12 out of 16 patients (75%) were in disease remission at study endpoint. **Conclusion:** In the present study, almost all patients were white females and the disease relapse rate was high.

Keywords: amino acyl tRNA synthetases, epidemiologic studies, interstitial lung disease, myositis.

INTRODUCTION

Antisynthetase syndrome (ASS) is an idiopathic inflammatory myopathy and chronic, systemic autoimmune disease with the presence of antisynthetase antibodies such as anti-Jo-1.¹⁻³

The anti-Jo-1 ASS is characterized by systemic involvement of muscle (myositis), lungs (interstitial lung disease) and articulation (chronic polyarthritis) besides fever, Raynaud's phenomenon and "mechanical hands".¹⁻³

Since it is a rare syndrome, its prevalence in the general population is unknown. Moreover, ASS epidemiological studies⁴⁻⁶ are scarce in the literature, except for a few case reports and serial cases.^{3,7-11}

Therefore, we reported a cohort retrospective study of 18 patients with anti-Jo-1 ASS from our tertiary service.

PATIENTS AND METHODS

Eighteen consecutive patients with anti-Jo-1 ASS followed at our Myopathy Unit between 1980 and 2010 were analyzed. All patients fulfilled Bohan & Peter criteria¹² had positive sera for anti-Jo-1 and involvement of muscle, lungs and articulations.

The study was approved by the local research ethics committee (HC n° 0039/10). The demographic features, treatment, clinical and laboratory data were obtained from patients' files.

The laboratory exams analyzed were performed at initial disease diagnosis and before corticosteroid use. Creatine-kinase (normal range: 24 - 173 U/L), lactic dehydrogenase (normal range: 20 - 350 U/L), aminotransferase alanine (normal range: 10-36 U/L), aminotransferase aspartate (normal range: 10-36 U/L) and aldolase (normal range: 1.0 - 7.5 U/L) were

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determined by the automated kinetic method. Antinuclear antibody (ANA) was determined by indirect immunofluorescence using Hep-2 cells as substrate. The Anti-Jo-1 antibody assay was performed using the immunoblotting technique. Anti-Ro and anti-La antibodies were analyzed by counterimmunoelectrophoresis against dog spleen.^{13,14}

Supplementary exams (thoracic radiography, thoracic computerized tomography, electrocardiogram, electromyography, and muscle biopsy of bicep arm muscle) were performed as routine procedure at initial medical consultations.

Disease recurrence was defined as the recurrence of initial clinical features and/or increased muscle enzymes attributed to disease activity, progression of pulmonary lesions (clinical and radiographic), after ruling out neoplasia or infection.

Corticosteroid therapy was the initial therapy used (prednisone, 1 mg/kg/day, oral) for 4-6 weeks followed by progressive tapering according to clinical and laboratory results. In severe cases (progressive dyspnea, dysphagia, significant loss of muscle strength) pulse therapy was performed with methyl-prednisolone (1 g/day for 3 consecutive days). The immunosuppressives used were azathioprine (2-3 mg/kg/day), methotrexate (20-25 mg/week), cyclosporine (2-5 mg/kg/day), mycophenolate mofetil (2-3 g/day), leflunomide (20 mg/day), monthly cyclophosphamide (0.5-1.0 g/m² intravenous) and chloroquine diphosphate (4 mg/kg/day).

Results were expressed as mean \pm standard deviation (SD) or as percentages.

RESULTS

Eighteen consecutive patients were analyzed over a period spanning 30 years. Table 1 shows demographic, clinical and laboratory features of patients.

Anti-Jo-1 ASS predominantly affected white (100%) females (94.4%) aged between 21 and 80 years, with average disease duration of 10 years.

The time of following up/duration of disease were 9.7 \pm 7.0 years. Constitutional symptoms occurred in 72.2% of cases. Cutaneous involvement was observed in 66.7%, while gastrointestinal tract involvement was seen in 55.6%.

Electromyography was carried out in all patients but inflammatory myopathy patterns were detected in 14 cases. Muscle biopsy was done in 11 patients, all of which presented anatomopathological alterations consistent with inflammatory myopathy.

Among autoantibodies, anti-Ro was present in two patients (11.1%) with basal pulmonary fibrosis, who had no history of disease relapse.

Table 1. Demographic features and clinical-laboratory data of patients with anti-Jo-1 antisynthetase syndrome

Age* \pm SD, variation (years)	39.9 \pm 15.7 (21-80)
Duration of disease \pm SD, variation (years)	9.7 \pm 7.0 (0-30)
Sex: female (%)	17 (94.4)
Ethnicity: white (%)	14 (100)
Clinical manifestation	
Constitutional symptoms (%)	13 (72.2)
Weight loss (%)	9 (50.0)
Fever (%)	10 (55.6)
Raynaud's phenomenon (%)	12 (66.7)
Pulmonary	
Dyspnea (%)	15 (83.3)
Dysphonia (%)	3 (16.7)
Cutaneous** (%)	12 (66.7)
Gastrointestinal tract involvement (%)	10 (58.8)
Dysphagia (%)	4 (22.2)
Dyspepsia (%)	6 (33.3)
Supplementary exams	
Antibodies	
Antinuclear (%)	10 (55.6)
Anti-Ro (%)	2 (11.1)
Muscle enzyme level	
Creatine kinase (U/L)	6,537.8 \pm 7,524.3
Aldolase (U/L)	34.2 \pm 28.0
Lactic dehydrogenase (U/L)	1,213.0 \pm 1,078.1
Aminotransferase alanine (U/L)	219.0 \pm 280.8
Aminotransferase aspartate (U/L)	262.1 \pm 338.2
Computed tomography	
Incipient pneumonia (%)	8 (44.4)
Ground-glass lesion (%)	12 (33.7)
Micronodules (%)	0
Basal fibrosis (%)	7 (38.9)
Pulmonary function test	
Restrictive pattern	6 (33.3)
Low carbon monoxide diffusion	1 (5.6)
Electrocardiogram – alteration (%)	0
Pulmonary hypertension (%)	1 (5.6)

*age at disease onset; **cutaneous: ulcers, calcinosis, vasculitis, rash. "mechanical hands"; SD: standard deviation;

In relation to pulmonary images, at least half of the patients evidenced incipient pneumopathy, ground-glass lesions and/or basal pulmonary fibrosis. There was one case of bronchiolitis obliterans with organizing pneumonia (BOOP), which had a good outcome after corticosteroid treatment. Restrictive pattern in pulmonary function test was observed in 33.3%. One patient presented with pulmonary hypertension (based on echocardiogram) and there were no cases of cardiac alterations (electrocardiogram).

Concerning comorbidities, systemic arterial hypertension was observed in 22.2% of cases, dyslipidemia in 5.6%, and diabetes mellitus not associated to corticosteroid therapy in 5.6%. One (5.6%) tuberculosis and three (16.7%) zoster herpes cases were detected. Neoplasm occurred in one (5.6%) case, confirmed as non-Hodgkin lymphoma. In this case, the neoplasm preceded ASS which manifested one year after chemotherapy.

No cardiovascular events were reported (coronary syndrome, deep venous thrombosis or stroke). During the following up, one patient died due to septic shock (hospital bronchopneumonia).

In relation to initial treatment, all subjects received corticosteroid (prednisone 1 mg/kg/day), and 12 patients (66.7%) received additional pulse therapy with methyl-prednisolone (1 g/day, 3 days). Various immunosuppressives were used (Table 2), depending on tolerance, side effects and refractoriness. Half of the patients (55.6%) used tapered corticosteroid (prednisone 0.2–1.0 mg/kg/day). Immunosuppressives used were: azathioprine (33.3%), methotrexate (33.3%), chloroquine diphosphate (22.2%), mycophenolate mofetil (16.7%), cyclosporine (16.7%), leflunomide (5.6%) and parenteral cyclophosphamide (11.1%), as monotherapy or in association.

Disease relapse (clinically and/or on laboratory exams) occurred in more than 2/3 of the cases. In the present cohort, the majority of the patients (75.0%) were in disease remission, but only two (11.2%) without the use of any drugs.

DISCUSSION

This study presented features of 18 patients with anti-Jo-1 ASS, a rare entity with few epidemiological reports in the literature.⁴⁻⁶ Therefore, the present study provides an overview of anti-Jo-1 ASS.

ASS affects mainly adult individuals at a ratio of 2.3 females : 1 male.^{1,15} All of our patients were aged over 18 years at disease onset, and our cohort included only one male.

ASS can present antibodies against different aminoacyl-tRNA synthetases. These cytoplasmatic proteins belong to the enzyme family whose function is to catalyze the bonding of specific aminoacids to respective tRNA.^{2,16} The presence of these antibodies is found in approximately 20–40% of polymyositis and 5% of adult dermatomyositis. The most frequent is anti-Jo-1 against histidyl-tRNA synthetase.¹⁷⁻¹⁹ In the present study, only ASS with anti-Jo-1 was assessed.

The clinical manifestation of ASS is relatively homogeneous with one or more of the following features: myositis, interstitial pulmonary disease and articular involvement. The presence of fever, Reynaud's phenomenon and "mechanical hands" may also be observed.^{18,19}

The muscle feature is found in more than 90% of cases with manifestation of myalgia, muscle weakness, atrophy and fibrosis. The initial general symptom involves proximal muscle of members.¹ These alterations are evident on muscle biopsy, electromyography and muscle enzyme increasing. Our

Table 2. Initial treatment used in patients with anti-Jo-1 antisynthetase syndrome at disease onset and outcome evaluation

Therapy	
Corticosteroid (%)	12 (33.7)
Azathioprine (%)	13 (72.2)
Methotrexate (%)	11 (61.1)
Cyclophosphamide (%)	9 (50.0)
Cyclosporine (%)	7 (38.9)
Chloroquine diphosphate (%)	5 (27.8)
Leflunomide (%)	2 (11.1)
Mycophenolate mofetil (%)	3 (16.7)
Clinical evaluation	
Stable (present) (%)	12/16 (75.0)
Recurrence (%)	14/16 (87.5)

patients showed muscle enzyme increase, while myalgia and/or muscle weakness occurred in 94.4% of cases.

Pulmonary involvement is found in more than 60% of cases and is the main cause of morbidity^{20,21} where this involvement can occur in the absence of muscle alterations. Therefore, in some cases interstitial pulmonary disease is predominant in ASS. This can show rapid onset and lead to acute respiratory insufficiency. The condition sometimes is highly refractory to standard treatment.^{22,23} Features include dyspnea, cough, thoracic pain, intolerance to physical exercises and respiratory insufficiency.²¹ Pulmonary radiography images can reveal an interstitial pattern. Ground-glass pulmonary lesion, linear opacities, consolidations parenchymal, micronodules can also be seen on computed tomography.^{21,24} The pulmonary function test shows a restrictive pattern. Patients with BOOP generally have a more favorable prognosis compared to those with diffuse alveolar lesions or interstitial pneumonia.^{25,26} In our patients, there was one patient with clinical findings consistent with BOOP who had a good outcome after corticosteroid therapy. The presence of pulmonary hypertension is reported in the literature and is associated to interstitial pulmonary disease.²⁷ There was one pulmonary hypertension case in our case series.

The presence of anti-Ro antibody has been associated to pulmonary fibrosis in ASS.^{5,6} We had two patients with the anti-Ro antibody. One of these had pulmonary fibrosis, but had a good response to corticosteroid and cyclophosphamide therapies. Neither of these patients had symptoms of *sicca* syndrome.

Articular involvement affects 50% of cases, with arthralgia and/or arthritis, with or without bone erosions. All our patients showed articular symptoms at disease onset.

Raynaud's phenomenon, "mechanical hands", photosensitivity, malar rash may also be present. Cutaneous vasculitis has been also described.²⁸ Cardiac involvement has also been observed, but its prevalence appears not to differ from that of polymyositis/dermatomyositis.²⁹ In the present study, two thirds (2/3) of the patients showed cutaneous alterations. No cases of cardiac involvement were found. Although there were no cases involving renal disease in the present study, mesangial proliferative glomerulonephritis has been described in ASS, where its manifestation is rare and has a good prognosis.³⁰

Corticosteroid therapy is the first-line treatment for myositis and also for interstitial pneumopathy in ASS. In the present study, all patients used corticosteroid. Moreover, half of the patients needed pulse therapy with corticosteroid, principally due to pulmonary involvement. With regard to immunosuppressive use, no consensus has been reached. The available evidence is weak, being based on case reports and reviews^{27,33,35,37-39} The most routinely used immunosuppressives are cyclophosphamide, azathioprine, mycophenolate mofetil, cyclosporine and tacrolimus. In this study, immunosuppressives were chosen based on tolerance, side effects and refractoriness.

After corticosteroid administration, all patients had initial remission of disease, in contrast to literature reports which describe a remission rate of between 21% and 68%.^{31,32} This discrepancy may be explained by the more frequent use of pulse therapy with corticosteroid in the present study. However, a higher frequency of disease relapse (82.4%) was found in the present study compared to rates reported in the literature (6% to 43%)^{31,32} Notwithstanding, the majority of patients remained stable and presented no further disease activity.

The mortality rate ranges from 12 to 40%.^{4,31,33,34} Furthermore, positive anti-Jo-1 and/or interstitial pneumopathy as prognostic factors remain controversial.³⁴⁻³⁷ In our patients, there was one death attributed to septic shock (hospital bronchopneumonia).

In conclusion, anti-Jo-1 ASS in our population predominantly affected white adults of female gender. A high rate of disease recurrence was observed along with the need for long-term use of corticosteroid and immunosuppressive therapy, but the majority of patients remained stable clinically and on laboratory exams up to the study endpoint.

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