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Epidemiological, clinical and immunological aspects of antisynthetase syndrome: a multicentre study in Dakar

Baïdy Sy Kane[1], Ahmadou Bamba Mbodji[2*], Mouhamed Dieng[1], Christelle Sabrina Yando Longo[1], Biram Codou Fall[3], Awa Cheikh Ndao[1], Moustapha Niasse[4], Adama Berthe[5], Maimouna Sow[1], Fatimata Ly[6], Souhaibou Ndongo[3] and Abdoulaye Pouye[1]

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Introduction

Idiopathic inflammatory myopathies (IIMs) or idiopathic-acquired myopathies represent a heterogeneous group of rare autoimmune diseases [1–3]. This group is made up of a set of acquired muscular disorders resulting from the dysregulation of the immune system. They can sometimes be associated with extramuscular autoimmune manifestations or cancer [1, 4]. The understanding of the pathophysiology of IIMs, their serological and histological specificity and above all the recent advent of myositis-specific autoantibodies (MSAs) have contributed to refining their classification. This classification, which is not unanimously accepted, includes dermatomyositis, inclusion myositis, autoimmune necrotising myositis and overlapping myositis and antisynthetase syndrome (ASS) and myositis associated with connective tissue disease [2, 4, 5]. ASS is characterised by muscle weakness, diffuse interstitial lung disease (ILD), polyarthritis, skin damage such as "mechanic's hands" and, to a lesser extent, Raynaud's phenomenon. Biologically, it is associated with autoantibodies of the antisynthetase family, the most frequent being the anti-Jo1 [6]. Studies on ASS are not numerous in sub-Saharan Africa. In Senegal, only two case-report studies have been published concerning this condition [7, 8]. In this context, we conducted a multicentric and descriptive study about epidemiological, diagnostic and immunological aspects of ASS.

Patients and methods

Patients

The aim of our study was to describe the epidemiological, clinical and immunological characteristics of patients with ASS followed in six major hospitals in Senegal. This was a retrospective, multicentre and descriptive study from 1 January 2014 to 30 June 2020 in four internal medicine departments, one pneumology department and one dermatology department of the following hospital centres: Aristide Le Dantec Hospital, Pikine National Hospital, Hospital Principal of Dakar, Dalal Jam National Hospital, Hygiène Social Institute and Regional Hospital of Thies. Our patients had been seen in the above-mentioned departments. In this study, patients who met the diagnostic classification of Solomon et al. [9] were included, namely the presence of an anti-aminoacyl-tRNA (ribonucleic acid) synthetase antibody plus two major criteria or one major and two minor criteria. Patients with incomplete records were excluded from the

*Correspondence:
Ahmadou Bamba Mbodji
mbodjahmadoubamba@gmail.com
[1] Department of Internal Medicine, Le Dantec Teaching Hospital, Cheikh Anta DIOP University, Dakar, Senegal
[2] Department of Neurosciences, Fann Teaching Hospital, Dakar, Senegal
[3] Department of Internal Medicine, Dalal Jam Hospital, Cheikh Anta DIOP University, Dakar, Senegal
[4] Department of Rheumatology, Dantec Teaching Hospital, Cheikh Anta DIOP University, Dakar, Senegal
[5] Department of Internal Medicine, Thies Regional Hospital, Thies, Senegal
[6] Department of Dermatology, Institute of Social Hygiene, Dakar, Senegal

study. An informed written consent has been obtained for all patients of the study.

Data

Data collection was done using a pre-established data collection form. The data included marital status, history, patient condition (cancer, connective tissue disease, infections, others) and treatment history. The physical examination was used to describe the characteristics of muscle involvement (topography, distribution, existence of amyotrophy) and to assess the characteristics of joint damage (topography, distribution, joint deformities, the presence of inflammatory signs such as synovitis). Pulmonary involvement was assessed by the existence of dyspnoea, oxygen saturation and the presence of crackling rales. Upon the dermatological examination, the existence of hyperkeratosis of the hands and feet and the existence of Raynaud's syndrome were assessed. The physical examination was complete to look for other disorders. The biological data collected were as follows: haemoglobin level, sedimentation rate, C-reactive protein (CRP) level and creatine kinase (CK) level.

The following immunological markers were investigated: anti-amino acyl RNA synthetase antibodies (anti-Jo-1; anti-PL-7; anti-PL-12; anti-EJ; anti-OJ; anti-ZO; anti-KS; anti-YRS, anti-JS and anti-SC) by dot-myosite; anti-extractable nuclear antibodies (anti-Sm; anti-SSA; anti-SSB; anti- RNP; anti-Scl-70); anti-PM-Scl; anti-double-stranded deoxyribonucleic acid (anti-dsDNA) and antinuclear antibodies.

Chest computer tomography (CT) was used to assess pulmonary involvement such as ILD (interstitial lung disease), their type and extension. Other paraclinical investigations were about electromyogram (EMG), electrocardiogram (EKG), respiratory test function and cardiac ultrasound. The therapeutic data collected at the time of diagnosis concerned corticosteroid therapy, immunosuppressants, physiotherapy and patient education (PE).

Statistical analysis

The data were recorded and analysed using SPSS (Statistical Package for the Social Sciences) software version 26.0. The results were expressed as a mean (+/− standard deviation) and median (with extremes) for the continuous variables and as percentages for the categorical variables. Means were compared using t Student, and comparisons between categorical measures were made using chi-square test. The comparison between categorical variables was made using the chi-square test. The p-value < 0.05 was considered statistically significant.

Table 1 Clinical presentation of 14 ASS patients

Clinical symptoms	Number	Percentage (%)
Muscle pain	10	71.4
Muscle weakness	10	71.4
Polyarthralgia/polyarthritis	12	85.7
Raynaud's syndrome	3	21.4
Fever	4	28.6
Physical signs	**Number**	**Percentage (%)**
Muscle weakness	13	93
Joint involvement	12	85.7
Acute polyarthritis	5	35.72
Chronic polyarthritis	7	50
Respiratory involvement	12	85.7
Cough/dyspnoea	8	57.14
Crackling rales	12	85.7
Specific dermatological conditions	7	50
Mechanics' hands	7	50
Hiker's feet	2	14.3

Table 2 Different immunological tests of 14 AAS patients

Immunology	Number	Percentage (%)
Anti-Jo1	10	71.43
Anti-PL12	3	21.43
Anti-PL7	1	7.14
Anti-NXP2	1	7.14
Antinuclear antibodies	8	57.14
Anti-SSA	9	64.29
Anti-Sm	1	7.14
Anti-RNP	1	7.14
Rheumatoid factor	1	7.14

Results

From 1 January 2014 to 30 June 2020, 14 patients (3 males and 11 females) were included in the study, whose main clinical, biological and radiological manifestations are summarised in Table 1. The sex ratio was 0.27, and the mean age of our patients was 44.07 years (+/− 10.43) with extremes between 24 and 58 years. The mean diagnostic delay was 22.71 months (+/− 34.79 months) (Tables 2, 3 and 4).

In our series, 2 of our patients (14.3%) had hypertension as a comorbidity. It should also be noted that 2 patients (14.3%) were initially classified as having dermatomyositis and polymyositis, without histological or immunological evidence. A family history of inflammatory arthritis was found in 2 patients (14.3%).

Muscle manifestations were present in all our patients with proximal and symmetrical weakness in

Table 3 Chest CT of AAS patients

Chest CT	Number	Percentage (%)
Non-specific ILD	9	64.29
Fibrosing non-specific ILD	2	1.28
Unclassifiable ILD	1	7.14

ILD interstitial lung disease

11 patients (78.6%). Distal and symmetrical weakness was present in 2 patients (14.3%); the last one had only myalgias. In our series, acute inflammatory arthritis concerned 5 patients (35.7%), while chronic polyarthritis constituted 7 patients (50%). Joint involvement concerned large and small joints in 12 patients (85.7%). Raynaud's syndrome was a non-specific dermatological condition noted in 4 cases (28.5%), while specific dermatological (Figs. 1 and 2) manifestations were present in 7 patients (50%).

Laboratory tests showed non-specific inflammatory syndrome in 10 cases (71.42%). The mean CRP levels were 87.25 mg/l (+/−132.14 mg/l). We had 12 patients (85.7%) with elevated CK at the time of diagnosis of ASS; the mean CK level was 5259 U/l (+/−5885.65 UI/l). The immunological workup showed anti-Jo1 autoantibodies in 10 patients (71.43%), anti-PL12 autoantibodies in 3 patients (21.4%) and anti-PL7 autoantibodies in 1 patient (7.1%). We did not find any statistically significant relationship between the clinical presentation and the distribution of antibodies.

EMG was described as myositis in 9 patients (64.3%). Muscle biopsy and muscle MRI were not performed in our series. Of the 8 patients (57.15%) who had a chest X-ray, five had interstitial syndrome. Chest CT scans were performed in 12 patients (85.72%) and showed non-specific ILD in 9 patients (64.3%), fibrosing ILD in 2 patients (14.3%) and unclassifiable ILD in 1 patient (7.1%) (Fig. 3).

Of the 2 patients (14.3%) who had an exploration of respiratory function, one case of obstructive syndrome and one case of mixed syndrome (obstructive and restrictive) were identified. Echocardiography of four patients showed circumferential pericardial detachment, septal hypertrophy with pericardial effusion, hyperkinetic heart with moderate arterial pulmonary hypertension or moderate tricuspid insufficiency. Corticosteroid therapy was used as first-line therapy for all patients. In our series, 13 patients (93%) of cases had received the combination of corticosteroid therapy and immunosuppressants such as azathioprine, methotrexate and hydroxychloroquine.

Discussion

We report here for the first time, to our knowledge, a multicentre study of ASS in sub-Saharan Africa. It identified 14 patients. Our series is relatively limited, it is consistent with the literature and the prevalence of this condition remains unknown in sub-Saharan Africa.

The preponderance of women in our series is similar to the literature. Although ASS is a condition that can occur at any age, the average age in our series was lower than that of Gusdorf et al. [10]. Compared to the literature [11], the patients in our series showed a delay in diagnosis. This could be explained by methodological differences or by a lack of knowledge of the disease in our region.

It should be noted that, as in most cohorts [6, 12] and our cohort, muscle involvement was present in all patients. This could be explained by various factors, such as the long delay in diagnosis or the immunological or ethnogenetic profile. We did not assess any correlation between anti-Jo titre and disease activity as reported by Stone et al. [13].

Joint manifestations were found in 85.7% of cases ($n=12$). They consisted of acute polyarthritis in 5 patients (41.6%) and chronic polyarthritis in 7 patients (53.4%). These data are similar to those found in the literature [11, 14]. They are close to the data of Meyer et al., who in their study reported 88% of cases with polyarthralgia and/or polyarthritis in 17 cases of antisynthetase syndrome associated with rheumatoid arthritis and positive anti-citrullinated peptides antibodies.

Interstitial lung disease (ILD) was present in 12 of our patients and was dominated by non-specific lung disease (64.3%). This pattern had been found by other authors [15, 16] but in varying proportions. However, the evaluation of the degree of extension was not noted in our study, although this is an important parameter for monitoring the evolution of ILD in ASS patients with pulmonary involvement.

In the literature, mechanic's hands are seen 19 to 56.5% of cases [6, 17]. Our data indicate that mechanic's hands were seen in 50% of cases and hiker's feet in 14% of cases. Gusdorf et al. study reported a lower frequency of mechanic's hand among cases of ASS.

In our study, we noted that 28.6% of cases had Raynaud's phenomenon, while incidence of Raynaud' phenomenon ranged from 28 to 93% in other studies [14, 15]. The frequency of this vasculopathy can be explained pathophysiologically by the activation of endothelial cells by anti-Jo1 antibodies [18]. We noted anti-Jo1 antibodies in 10 patients (71.4%).

The presence of anti-SSA antibodies is considered a factor in the severity of lung parenchyma, muscle and joint involvement [15, 19]. They were found in 9 of our

Table 4 Main characteristics of the patients

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Age	52	49	44	58	34	24	55	58	54	37	39	35	41	37
Gender	F	F	F	M	F	F	H	F	F	F	F	F	H	F
Diagnostic delay (month)	12	7	21	8	6	3	135	6	12	12	36	6	6	48
Muscle manifestations	Muscle weakness	Myalgia, muscle weakness	Myalgia, muscle weakness	Myalgia, muscle weakness, dysphagia	Muscle weakness	Myalgia, muscle weakness	Muscle weakness	Muscle weakness	Myalgia,muscle weakness	Myalgia, muscle weakness	Myalgia, muscle weakness	Myalgia, muscle weakness	Myalgia	Myalgia, muscle weakness
Extra muscular manifestations	Arthritis, mechanic's hands	Arthritis, cough, crackling rales, Raynaud, fever	Arthritis, dyspnoea, crackling rales, periorbital erythema	Arthritis, fever, dyspnoea, crackling rales, vesico-bullous skin lesions	Arthritis, mechanic's hands, Hiker feet, dyspnoea, crackling rales	Arthritis, crackling rales, erythroderma, fever	Arthritis, mechanic's hands, Raynaud's, crackling rales	Arthritis, dyspnoea, cough, crackling rales, mechanic's hands, panniculitis, hyperkeratosis of the nasal wings	Arthritis, dyspnoea, crackling rales, keratoderma	Arthritis, cough, dyspnoea, crackling rales, keratoderma, Raynaud, mechanics' hands, fever	Cough, dyspnoea, crackling rales, mechanic's hands, Hiker feet	Arthritis, cough, crackling rales	Arthritis, cough, crackling rales, keratoderma	Keratoderma, mechanic's hands, sclerodactyly, microstomy
CK (UI/l)	5620	1032	1204	11,372	3268	20,170	NA	317	9509	5088	2020	NA	3337	139
Antisynthetase autoantibodies	Jo1	Jo1	PL12	Jo1	Jo1	Jo1	Jo1	PL7	Jo1	Jo1	PL12	PL12	Jo1	Jo1
Other autoantibodies	SSA	SSA	RF	ANA, SSA	None	ANA	SSA	SSA	ANA, SSA	ANA, SSA	ANA, SSA, anti-Sm U1RNP, NXP2	SSA, ANA	ANA	ANA
CT chest	uILD	ns lLD	nsILD	Fib	Fib	nsILD	None	nsILD	nsILD	nsILD	nsILD	nsILD	nsILD	None
Treatment	C, AZA, HQ	C, AZA	C, AZA	C, MTX	C, AZA, HQ	C, AZA, HQ	C, AZA	C, AZA	C, AZA, MTX	C, AZA	C, MTX	C, AZA	C, AZA	C, MTX
Associated systemic autoimmune disease	None	Sjogren's syndrome	None	None	Sjogren's syndrome	None	Sjogren's syndrome	None	None	Systemic sclérosis	None	None	None	None

C corticosteroid therapy, *HQ* hydroxychloroquine, *AZA* azathioprine, *MTX* methotrexate, *RF* rheumatoid factors, *n.s.ILD* interstitial lung disease, *Fib* fibrosing non-specific ILD, *uILD* unclassifiable ILD, *ANA* antinuclear antibodies, *NA* not available

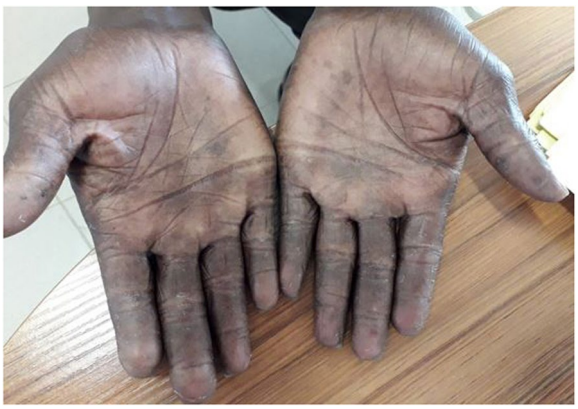

Fig. 1 Mechanic's hand in our patient. Hyperkeratosis of the fingers associated with hyperpigmentation

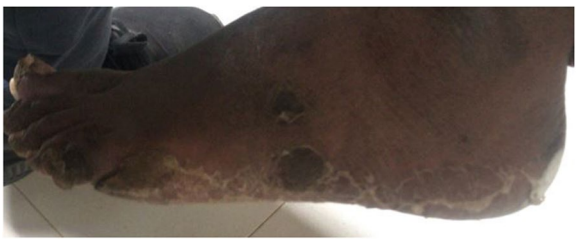

Fig. 2 Plantar keratodermia. Plantar erythematous-squamous lesion

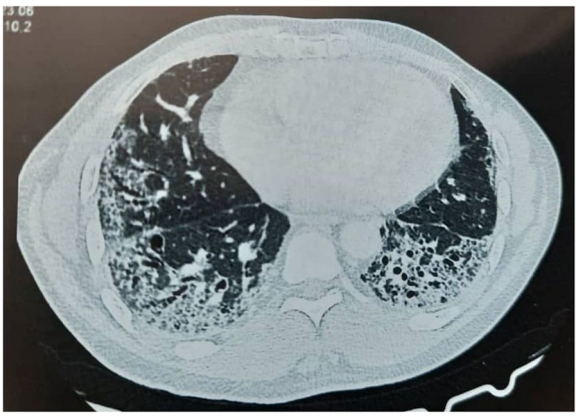

Fig. 3 Chest computer tomography Interstitial Lung disease in our patient

cases (64.3%). These results are higher than those of Dieval et al. who reported anti-SAA antibodies in50% of cases.

However, we did not find any statistically significant relationship between the clinical presentation and the distribution of antibodies.

The routine use of immunoblot for the detection of MSAs in IIMs has resulted in a significant number of multipositive cases [20]. We noted only one case (7.1%) of multipositivity of autoantibodies specific for myositis in our series. One patient had anti-NXP2 and anti-PL12. A reasoned prescription, collaboration between biologists and clinicians and a critical interpretation of the immunoblot seem essential.

The treatment of ASS is not yet codified [19, 21]. In general, treatment of ASS should be targeted according to the clinical phenotypes and symptom severity of the ASS [16, 22]. In our study, 13 patients were treated with corticosteroids at the time of diagnosis. The immunosuppressive drugs prescribed in association with corticosteroid therapy in our patients were azathioprine in seven cases, methotrexate in two cases and the combination of methotrexate and azathioprine in three cases. Methotrexate and azathioprine have similar efficacy in ASS [23], but methotrexate is often avoided in patients with severe ILD.

One of the limitations of our study is the retrospective nature of recruitment. This may have led to statistical biases due to missing data on parameters in some patient files. The second limitation is the relatively small size of our sample. However, it allowed us to highlight a clinical and immunological profile of ASS in our region.

Conclusion

ASS is a rare and heterogeneous connective tissue disease. Although retrospective, our multicentre study confirms the fact that ASS is a condition that predominates in young women with variable manifestations but dominated by muscular, articular and pulmonary involvement. It is often associated with the presence of antisynthetase antibodies, particularly against Jo1. Better knowledge of this syndrome by organ specialists would reduce the time taken to diagnose the disease, improve patient management and thus avoid the occurrence of the major complication of this syndrome, i.e. pulmonary fibrosis.

Abbreviations

IIMs	Idiopathic inflammatory myopathies
MSAs	Myositis-specific autoantibodies
ASS	Antisynthetase syndrome
RNA	Ribonucleic acid
CRP	C-reactive protein
CK	Creatine kinase
Chest CT	Chest computed tomography
ILD	Interstitial lung disease
EMG	Electromyogram
ECG	Electrocardiogram
PE	Patient education
SPSS	Statistical Package for the Social Sciences
MRI	Magnetic resonance imaging
C	Corticosteroid therapy
HQ	Hydroxychloroquine
AZA	Azathioprine
MTX	Methotrexate
RF	Rheumatoid factors
n.s.ILD	Non-specific interstitial lung disease

Fib	Fibrosing non-specific ILD
uILD	Unclassifiable ILD
ANA	Antinuclear antibodies
NA	Not available

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Authors' contributions
BSK, designed, coordinated this research and participated to the correction of the document. ABM, drafted the manuscript. MD, CY, SL, BCF, ACN, MN, AB, MS, FL, SN and AP, these authors participated in research coordination and the correction of this document. All authors approved the final manuscript and agreed with the publication of the document.

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Declarations

Ethics approval and consent to participate
The ethical committee of the university gave the agreement to this study.

Consent for publication
Written informed consent was obtained from the patients for publication of this study and accompanying images. A copy of the written consent is available for review by the editor in chief of this journal on request.

Competing interests
The authors declare that they have no competing interests.

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