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Profile of Autoimmune Polyendocrinopathies at the Medical Clinic II of the Abass Ndao Hospital: About 40 Cases

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Abstract

Introduction: Autoimmune polyendocrinopathies (AP) represent a group of rare concomitant pathologies, making them underdiagnosed. The objective was to study their profile at the Medical Clinic II of the Abass Ndao Hospital. **Patients and Methods:** This was an observational, descriptive and analytical study, lasting 24 months, from January 1, 2020 to December 31, 2022. We assessed the epidemiological, clinical and paraclinical characteristics of the patients and classified the APs found. **Results:** We included 40 patients divided into type III (38 cases) and IV (2 cases). A female predominance was noted with a sex ratio of 0.21. The mean age was 38.6 years. A family history of component diseases of autoimmune polyendocrine syndrome (APS) was found in 62.5%. Goiter (80%) was the main clinical sign present. All 38 patients with ISAP-3 had autoimmune thyroiditis, including 29 cases of Graves' disease (72.5%) and 9 cases of Hashimoto's thyroiditis (22.5%). They were associated with either type 1 diabetes (57.9%), Biermer's disease (21.1%), vitiligo + alopecia (18.4%), lupus (2.6%). The 2 patients with AP-4 had Biermer's disease associated with either Addison's disease or type 1 diabetes. Management depended on the pathologies present and their possible complications. The immunological phenomena were also controlled. **Conclusion:** This series is globally similar to the literature. The polymorphous character of the clinical pictures requires a better collaboration between specialists leading to a clinical and holistic synthesis.

Keywords

APS, Biermer, Graves' Disease, Hashimoto's, Addison's, Vitiligo, Senegal

1. Introduction

Autoimmune polyendocrinopathies (AP) are diseases characterized by the coexistence of at least two endocrine disorders of autoimmune mechanism, sometimes associated with a non-endocrine autoimmune disorder [1]. These are rare conditions, with a clinical heterogeneity that makes them under-diagnosed. Since the 19th century, the medical community has known that certain individuals or their families can be affected by multiple endocrine alterations. Neufeld and Blizzard [2], after a series of observations and studies, proposed a classification based essentially on clinical findings in 1980. This classification is summarized in **Table 1**. Kahaly *et al.* [3] reported in a 2012 study of a German population that AP-2 was the most common form. In Finland, the prevalence of AP-1 has been estimated at 1/25,000 cases [4] [5]. In the United States, the prevalence of AP-2 has been estimated at around 20 per million inhabitants [6]. To date, epidemiological data on the different forms of AP are unknown in Africa and Senegal. A recent study of the association of autoimmune hypothyroidism with other autoimmune conditions in a department of internal medicine south of the Sahara reported 04 cases out of 24 AP recorded over a period of 05 years [7]. Against this background of under-reporting, we thought it would be useful to study the epidemiological, clinical and therapeutic profile of AP at the Medical Clinic II of the Abass Ndao Hospital in Dakar.

2. Patients and Methods

This was an observational, descriptive and analytical study carried out from January 1, 2020 to December 31, 2022 at the Medical Clinic II. This is a university hospital department specializing in the management of organ-specific autoimmune pathologies, particularly diabetes and hypothyroidism. Thus, all patients coming for consultation with an endocrinopathy of autoimmune origin were screened for other autoimmune conditions, depending on the context. With this in mind, we included all patients presenting with at least two autoimmune conditions, including an autoimmune endocrine condition and/or another autoimmune condition included in the AP classification. We excluded patients with incomplete investigations and those who could not be classified. Information was collected using a pre-coded, anonymous questionnaire designed by us, and patients were classified according to **Table 1** [2]. The parameters studied were:

- Socio-demographic data: age, sex, profession, marital status, behavioral measures (smoking, alcoholism), history and terrain (hypothyroidism, hypertension, diabetes, sickle-cell anemia), gyneco-obstetrical events;

- Clinical data: reasons for consultation, vitals and physical examination of all devices and systems;

- Paraclinical data: these data were sought according to profile and context. These included biology (blood count, vitamin B12, fasting blood glucose, HbA1c, 8-hour cortisol, TSHus, free T4), immunology (anti-R-TSH antibodies,

Table 1. Neufeld and Blizzard's 1980 modified classification of AP [2].

AP Type	Features
Type 1	Presence of at least 2 components such as chronic candidiasis, hypoparathyroidism, autoimmune Addison's disease
Type 2	Autoimmune Addison's disease + autoimmune thyroid disease and/or type 1 diabetes
Type 3	Autoimmune thyroid disease + other autoimmune diseases (excluding Addison's disease and hypoparathyroidism)
Type 4	Two or more organ-specific autoimmune diseases that do not fall into types 1, 2 or 3.

anti-TPO antibodies, anti-TG antibodies, antiintrinsic factor antibodies, anti-IA2 antibodies, anti-GAD antibodies, anti-nuclear antibodies, anti-DNA antibodies, anti-21-OH antibodies). Depending on the profile, we also performed thyroid ultrasound and scintigraphy, and oeso-gastro-duodenal fibroscopy.

- Therapeutic data: insulin therapy, synthetic antithyroid drugs, levothyroxine, cyanocobalamin (Vitamin B12), hydrocortisone, prednisone, hydroxychloroquine.

The various forms of AP were classified according to major criteria: Addison's disease, Graves' disease, Hashimoto's thyroiditis, type 1 diabetes; and minor criteria: hypogonadism, alopecia, vitiligo, Biermer's disease, chronic gastritis, intestinal malabsorption, Sjögren's syndrome, lupus disease, rheumatoid arthritis, celiac disease, autoimmune hepatitis, sarcoidosis [8].

Data entry was performed with Epi Info Version 7 software and analysis with SPSS Version 21. Thus, qualitative variables were described by frequency tables, bar charts, and pie charts. Quantitative variables were described by their positional (mean, median and mode) and dispersion (standard deviation, extremes) parameters.

3. Results

3.1. Epidemiological Data

Of the 46 cases meeting the recruitment criteria, 40 files were exploitable and fulfilled the inclusion criteria, giving a completion rate of 86.9%.

Women represented 82.5% of the series, with a sex ratio of 0.21. The mean age was 38.6 ± 10 years (extremes 23 and 59 years). The majority of patients 87.5% (n = 35) had a professional activity, 10% had no profession and 2.5% were students. Ethnically, they were Wolofs (50%) and Alpoulars (25%). 3/4 of patients were married and 22.5% were single. Medical history and land were noted in 62.5%. The majority of the latter were diabetic (62.5%). Eleven (11) patients had had early abortions. Other medical conditions were ethyl (7.5%), active smoking (2.5%), arterial hypertension (4%) and sickle cell disease (4%).

3.2. Clinical and Paraclinical Data

Goitre (95%) was the main clinical sign, followed by exophthalmos (65%) and

cardinal syndrome (55%). Table 2 shows the distribution of patients according to clinical signs.

Ten (10) patients presented with macrocytic anemia and low vitamin B12 levels. TSHus, measured in 38 patients, was high in 9 and low in 29. Fasting blood glucose and HbA1c were elevated in 23 patients. Immunologically, anti-IA2 and anti-GAD antibodies were positive in 43.5%. Among patients who were tested for TSH receptor antibodies (n = 11), anti-thyroproxidase antibodies (n = 09), anti-thyroglobulin antibodies (n = 05) and anti-intrinsic factor antibodies (n = 06), 37.9%, 100%, 55.6% and 60% respectively were positive. Table 3 shows the distribution of patients according to test results.

Among patients with Graves' disease (n = 29 or 72.5%) and Hashimoto's thyroiditis (n = 9 or 22.5%), 27 had undergone thyroid ultrasound. All patients with Graves' disease showed a homogeneous, diffuse, hypervascularized goiter, while those with Hashimoto's thyroiditis showed a heterogeneous goiter over probable thyroiditis.

In the 10 patients (21.1%) with Biermer's disease, oesophageal-duodenal fibroscopy in 4 (40%) showed atrophic gastritis in all cases. Anatomopathological examination of gastric tissue in one patient revealed intense atrophic follicular antral and fundic gastritis with no evidence of dysplasia or metaplasia.

Table 2. Distribution of patients according to clinical signs.

Clinical signs	Effective	Frequency
Goiter	38	95%
Exophthalmos	26	65%
Cardinal syndrome	22	55%
Weight loss	16	40%
Pale mucous membranes	10	25%
Asthenia	10	25%
Hypometabolism syndrome	9	22.5%
Melanoderma	6	15%
Nausea, vomiting, diarrhea	6	15%
Palpitations	5	12.5%
Fever	5	12.5%
Alopecia	4	10%
Myxedematous syndrome	4	10%
Neuropsychiatric disorders	4	10%
Dyspnea	3	7.5%
Erythema	1	2.5%
Low blood pressure	1	2.5%
High blood pressure	1	2.5%
Polyarthralgias	1	2.5%

Table 3. Distribution of patients according to complementary investigations.

Biological data	Value	Effective	Frequency
Biochemical data			
Anemia	Yes	18	45%
Mean corpuscular volume	>100 fl	10	25%
B12 Vitamin	<145 pg/ml	10	25%
Fasting blood glucose	>1.26 g/l	23	57.5%
HbA1c	>6.5%	23	57.5%
Hormone data			
Cortisolaemia	<37 mg/ml	1	2.5%
TSHus	<0.01 mUl/l	29	72.5%
	>6 mUI/l	9	22.5%
Free T4	<9 pmol/l	9	22.5%
	>24 pmol/l	29	72.5%
Immunological data			
Anti-R-TSH antibodies	>1.5 UI/ml	11	37.9%
Anti-Thyreoperoxidase antibodies	>30 UI/ml	9	100%
Anti-Thyroglobulin antibodies	>25 UI/ml	5	55.6%
Anti-intrinsic factor antibodies	>1.53 UI/ml	6	60%
Anti-IA2 antibodies	>28 UI/ml	10	43.5%
Anti-GAD antibodies	>17 UI/ml	10	43.5%
Anti-nuclear antibodies	>1/80 UI/ml	1	100%
Anti-DNA antibodies	>1/80 UI/ml	1	100%
Anti-21-Hydroxylase antibodies	>54 UI/ml	1	100%

3.3. Classification According to Type of AP

On the basis of clinical and paraclinical investigations, we classified patients according to major and minor criteria.

- **Major criteria**: All patients had at least one of the major clinical criteria. These were Graves' disease (72.5%), type 1 diabetes (57.5%), Hashimoto's thyroiditis (22.5%) and Addison's disease (2.5%).

- **Minor criteria**: Eighteen patients (45%) had minor clinical criteria. Biermer's disease accounted for 55.6% of minor criteria, vitiligo + alopecia (38.9%); lupus disease (5.5%).

- **Classification according to the type of AP**

The majority of patients (95%) had type 3 AP and 5% had type 4 AP. Type 3 AP is subdivided into 4 subtypes. Most (57.9%) patients had subtype 3a. Subtypes 3b, 3c and 3d accounted for 21.1%, 18.4% and 2.6% respectively. Females accounted for 81.1% and 100% of cases for AP-3 and AP-4 respectively. The majority of AP-3 patients were under 40 years of age, whereas AP-4 cases were all over 40.

3.4. Therapeutic Data

Patients were treated for the various pathologies they presented. Complications included cardiothyreosis in 13.8% of cases, Graves' disease in 43.5%, ketoacidosis in 4.3% and retinopathy in 4.3% of patients with type 1 diabetes. Table 4 below shows the distribution of patients according to treatment received.

4. Discussion

4.1. Limitations of Our Study

The main limitation of our study was the patients' lack of means to perform certain immunological tests necessary for pathology classification.

4.2. Epidemiological Data

During the 15-month study period, 40 patients were recruited with autoimmune polyendocrinopathy. This work illustrates the low representativeness of this pathological group within our hospital institution in relation to the number of annual admissions. Within our population, 2 types of AP were found. These were AP-3 and AP-4. The absence of AP-1 and IPEX syndrome can be explained by their pediatric onset. As for AP-2, the few cases of Addison's disease did not meet the AP-2 criteria. The rarity of Addison's disease in our study contrasts with data from Kahaly *et al.* [3] in a German population. The latter reported that AP-2 was the most common form. In our series, it was AP-3 (95%).

Whatever the type of AP, the predominance of females was constant, with a sex ratio of 0.21. These prevalences were close to those found by Aung *et al.* [9] in 2007 for AP-3 and Betterle *et al.* [8] in 2001 for AP-4.

The mean age was 38.6 years, with a majority of subjects under 40 years of age for AP-3 and all over 40 years of age for AP-4. In a study by Rekik *et al.* [10], the mean age of patients with AP-3 was 39. Better *et al.* [8] had previously found a mean age of 30 years for patients with ISAP-4. The advanced age of our patients at diagnosis may be explained by the sometimes late diagnosis of pathologies within our structures. AP is characterized by clinical heterogeneity. Goiter was the main clinical sign (80%). This testifies to the frequency of thyroid pathologies in our facilities.

Table 4. Distribution of patients according to treatment received.

Drug treatment	Effective	Frequency
Insulin therapy (Mixtard®) 0.5 mg/kg/day	23	57.5%
B12 Vitamin 1000 µg/month	10	25%
Carbimazole 40 to 60 mg/day	29	72.5%
Hydrocortisone 20 to 40 mg/day	1	2.5%
Levothyroxine 1.6 to 1.7 µg/kg/day	9	22.5%
Prednisone 20 mg/day	1	2.5%
Hydroxychloroquine 3.5 mg/kg/day	1	2.5%
Propranolol 40 mg/day	4	10%

All our patients had major criteria, compared with 45% for minor criteria. The prevalence of the various diseases making up AP varied from one population to another. Indeed, according to a study by Betterle *et al.* [11] in an Italian population, there was 7% Hashimoto's disease, 60% Addison's disease, 10% type 1 diabetes, 15% Biermer's disease, 12% vitiligo, 37% alopecia. In another Norwegian series [11], type 1 diabetes (9%), vitiligo (20%) and alopecia (41%) predominated.

In addition to autoimmune thyroid disease, all AP-3 patients had either type 1 diabetes (type 3a with 57.9%), Biermer's disease (type 3b with 21.1%), vitiligo and alopecia (type 3c with 18.4%), or lupus disease (type 3d with 2.6%). This shows that a patient with autoimmune thyroid disease is likely to develop other autoimmune diseases in his or her lifetime, such as type 1 diabetes, Biermer's disease, vitiligo, alopecia and lupus. Bennour *et al.* [12], reported the frequent occurrence of autoimmune diseases, mainly autoimmune thyroiditis (61.5%), during the course of type 1 diabetic patients. The predominance of type 3a thyroiditis suggests that type 1 diabetic patients should be screened for autoimmune thyroiditis.

With regard to AP-4, we had two types of association: Addison's disease + Biermer's disease, then type 1 diabetes + Biermer's disease. This shows that associations that do not fall within the classic types of AP are possible. The study by Fraj *et al.* [13] in a population with Biermer's disease found associations with Addison's disease (7.6%) and type 1 diabetes (3.8%).

Optimal, holistic treatment and monitoring of AP remains the rule. Certain complications were noted in our study population. These included 13.8% cardiothyreosis among cases of Graves' disease, 43.5% ketoacidosis and 4.3% diabetic retinopathy among type 1 diabetics. Diagne *et al.* [14] and Diédhiou *et al.* [15], studying Graves' disease, found cardiothyreosis in 11.1% and 9.8% respectively. In type 1 diabetes, Sarr *et al.* [16] in Senegal and Balasubramanyam *et al.* [17] in black Americans with type 1 diabetes reported diabetic ketoacidosis as the main complication in 57% and 53% of cases respectively. Berrabeh *et al.* [18] in Morocco found diabetic retinopathy in 26.3% of patients with T1DM. This difference may be explained by the fact that ophthalmological investigations are not systematically performed in all cases of type 1 diabetes.

5. Conclusion

This series of AP is broadly similar to those reported in the literature in terms of epidemiological, clinical, paraclinical and therapeutic parameters. However, it differs in the high rate of AP-3 cases, a clearer female predominance, and a slightly higher mean age. The frequency of these pathologies remains unknown. This leads us to focus our attention on the systematic search for the coexistence of autoimmune endocrinopathies. Long-term monitoring, with thyroiditis and/or type 1 diabetes as the main gateway, is the key to diagnosis. Association with systemic autoimmune diseases remains rare.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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