PAI-BEL: A Belgian multi-centre survey of Primary Adrenal Insufficiency

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Abstract (247 words)

Objective: Primary Adrenal Insufficiency (PAI) is a rare disease with an increasing prevalence, which may be complicated by life-threatening adrenal crisis (AC). Good quality epidemiological data remain scarce. We performed a Belgian survey to describe the aetiology, clinical characteristics, treatment regimens, comorbidities and frequency of AC in PAI.

Methods: A nationwide multicentre study involving 10 major university hospitals in Belgium collected data from adult patients with known PAI.

Results:

200 patients were included in this survey. Median age at diagnosis was 38 years (IQR 25-48) with a higher female prevalence (F/M sex ratio=1.53). Median disease duration was 13 years (IQR 7-25). Autoimmune disease was the most common aetiology (62.5%) followed by bilateral adrenalectomy (23.5%) and genetic variations (8.5%). The majority (96%) of patients were treated with hydrocortisone at a mean daily dose of 24.5 ± 7.0 mg, whereas 87.5% of patients also received fludrocortisone. About one third of patients experienced one or more AC over the follow-up period, giving an incidence of 3.2 crises per 100 patient years. There was no association between the incidence of AC and maintenance dose of hydrocortisone. 27.5% of patients were hypertensive, 17.5% had diabetes and 17.5% had a diagnosis of osteoporosis-

Conclusion: This study provides the first information on the management of PAI in large clinical centres in Belgium, showing an increased frequency of postsurgical PAI, a nearly normal prevalence of several comorbidities, and an overall good quality of care with a low incidence of adrenal crises, compared with data from other registries.

Introduction

Primary adrenal insufficiency (PAI) is a rare disease, most commonly of auto-immune origin. There is a global variation in prevalence from 80 to 145 per million in Europe, with highest case numbers reported in Scandinavian countries (1) and lowest in Japan. Despite the advent of glucocorticoid replacement therapy in the early 1950s, life-expectancy remains lower than in the general population (2), with increased morbidity and impaired quality of life (3, 4). Increased mortality is due to factors either directly related to the disease such as fatal adrenal crisis (AC), indirectly related such as increased risk of cardiovascular disease or cancers, or due to complications of glucocorticoid treatment (5). Current clinical practice guidelines from the Endocrine Society recommend glucocorticoid replacement with either hydrocortisone (15-25 mg/day in 2-3 divided doses) or cortisone acetate (20-35 mg/day) and mineralocorticoid replacement with once-daily fludrocortisone at a starting daily dose of 50-100 μ g (6). However, there remains substantial heterogeneity in local practice, and there is as yet no evidence-based optimal glucocorticoid or mineralocorticoid regimen.

Given the rarity of PAI, there is a paucity of detailed and up to date information regarding epidemiology and incidence, aetiology, optimal treatment modalities and prevalence of acute and chronic complications. A number of studies have sought to address this gap (Table 1), including medication prescription surveys (7, 8), local registries or case series (9, 10), epidemiological studies (11, 12, 13, 14) and quality of life studies (15). In recent years, national registries have been reported in European (13, 16, 17) and Asian countries (18). A multinational European prospective registry (EU-AIR) is also underway (19), with the specific aim of determining optimal regimens and safety data for glucocorticoid replacement therapy.

We performed a Belgian survey of primary adrenal insufficiency (PAI-BEL) in 10 major Belgian university hospitals, in order to furnish data about PAI, including general epidemiology, type and doses of adrenal replacement therapies, metabolic co-morbidities and incidence of AC.

Materials and methods

PAI-BEL is an observational, multicentre, retrospective study to establish a survey of patients in Belgium with a diagnosis of primary adrenal insufficiency.

Hospitals and endocrinologists were approached by direct invitation as well through advertising at the annual congress of the Belgian Endocrine Society. Ten major hospitals including 6 out of the 7 Belgian academic centres and 4 large university-affiliated hospitals agreed to participate in the data collection. Data collection took place between 03/09/2015 and 31/12/2018. The study was approved by local ethics committees of each institution participating in the study and informed consent was waived due to the retrospective nature of the survey. Patients with a diagnosis of PAI were identified and enrolled in the study by the referent endocrinologists. Cases of congenital adrenal hyperplasia and secondary adrenal insufficiency were excluded as the former was considered a paediatric onset disease different from PAI and the latter as non-primary. The primary investigator confirmed the diagnosis of PAI by verifying the presence of either (a) initial clinical signs characteristic of PAI such as weight loss, gastro-intestinal symptoms and hyperpigmentation together with at least one of the following criteria: 1) a simultaneous serum level cortisol below and a plasma ACTH 2fold above reference ranges; 2) a high plasma ACTH concentration with a failed cortisol response (< 400nmol/L) to 250 µg intravenous ACTH injection, and/or 3) chronic treatment with glucocorticoids and fludrocortisone; or (b) a history of bilateral surgical adrenalectomy or of unilateral surgical adrenalectomy combined with chemical adrenalectomy by mitotane in 1 patient (diagnosis of PAI confirmed after long-term mitotane withdrawal). Patients were assigned a unique identification number for the purposes of the study and double reporting was excluded by comparing date of birth, sex and year of diagnosis. Data were collected

through anonymised case report forms completed by the referent endocrinologists. Data were reported on epidemiology, aetiology, clinical presentation at diagnosis, tests used for diagnosis, auto-immune status, current glucocorticoid and mineralocorticoid treatment regimens, incidence of AC (as defined by the clinician) and co-morbidity such as diabetes mellitus, hypertension and osteoporosis.

Statistical analysis was performed using GraphPad Prism version 6 software. The normality of the distributions of the quantitative data was evaluated with graphical representations (histogram, box plot and q-q plot). The mean and standard deviation (SD) were used to describe symmetrical distributions, while the median and interquartile range (IQR) were used for asymmetrical distributions. Distributions were compared between three groups with Kruskal-Wallis test and Dunn's test for multiple comparisons, and between two groups with Mann-Whitney-Wilcoxon test. For adult patients > 18 years, we compared BMI at survey with BMI at diagnosis using Wilcoxon signed-rank test. Frequencies were compared between groups with Pearson's chi-squared test or Fisher's exact test, depending on the expected frequencies. Spearman's correlation coefficient (r_s) was used to measure the correlation between parameters. The level of statistical significance was set at 0.05.

Results

206 patients first met inclusion criteria and were entered into the PAI-BEL registry. Four cases of double reporting and two cases of secondary adrenal insufficiency were excluded from the analysis bringing the total number of cases studied to 200. Considering an estimated mean prevalence of 100 cases/million in Western Europe, this would represent about one quarter of all adult Belgian patients with PAI.

Epidemiology

The median age at diagnosis was 38 years (IQR 25-48; min-max 0-82). 28 patients (14%) were below the age of 18 at the time of diagnosis. There was a higher prevalence in females

(F 121, M 79; sex ratio F/M=1.53). Median duration of disease at the time of data collection was 13 years (IQR 7-25, min-max 1-64).

Clinical presentation at diagnosis

Excluding patients in whom adrenal insufficiency was expected due to iatrogenic induction [bilateral surgery (n=47) and unilateral surgical adrenalectomy combined with mitotane chemotherapy (n=1)], the most common symptoms at diagnosis were fatigue (78%), weight loss (74%) and anorexia (63%) (Figure 1). Cutaneous hyperpigmentation was present in 63% and vitiligo in 7%. 52% of patients reported gastrointestinal symptoms. Hypotension was reported in 58% of cases, electrolyte disturbance in 46% and hypoglycaemia in 10%. Excluding patients younger than 18, median BMI at diagnosis was 23.5 kg/m² (IQR 20.1-27.0; min-max 14.5-43.8; n=127).

Diagnostic workup

43% of patients had high ACTH with low cortisol at diagnosis, while 29% of patients had a high ACTH level together with a positive corticotrophin stimulation test showing absent or insufficient cortisol stimulation above the cut-off of 400nmol/L. The vast majority of these patients had presented with a classic clinical picture of adrenal insufficiency, and 41.5% had adrenal and/or specific auto-antibodies against 21-hydroxylase. 24% of patients had a history of bilateral surgical adrenalectomy (or chemical in one) and 3.5% presented with an inaugural AC.

Aetiology

Autoimmune disease was the most common cause of PAI (62.5%), followed by bilateral adrenalectomy (23.5%), genetic variations (8.5%), adrenal haemorrhage (2%), tuberculosis (1.5%), amyloidosis (0.5%), unilateral adrenalectomy with combined mitotane chemotherapy (0.5%) and idiopathic (1%). We further analysed and compared the three commonest aetiologies (Table 2).

Auto-immune disease (AI)

In this group of 125 patients, the median age at diagnosis was 38 years (IQR 28-45; min-max 3-82) and the median duration of disease was 15 years (IQR 8-28; min-max 1-64). 55 patients (44%) were categorised as having isolated adrenal insufficiency, 2 (1.6%) as auto-immune polyglandular syndrome type 1 (APS 1), 67 (53.6%) as auto-immune polyglandular syndrome type 2 (APS 2) and one patient (0.8%) as idiopathic due to adrenal antibody negativity.

Seven patients (5.6%) were recorded as presenting with an inaugural AC. Adrenal and/or specific auto-antibodies against 21-hydroxylase were present in 79/96 patients (82%) for whom information was available. The most common associated auto-immune endocrinopathy was thyroiditis (66/115 patients, 57%) on the basis of the presence of auto-antibodies. 16 patients (13%) had a diagnosis of type 1 diabetes mellitus, 69% of whom had recorded auto-antibodies against GAD65. We recorded 30.5% (18/59) of anti-parietal cell antibodies and, in women, 16.7% (4/24) of anti-ovarian antibodies. Considering only patients with a diagnosis in adulthood (age > 18 years), BMI was significantly higher at last follow-up compared to diagnosis (P < 0.0001). The median change over follow-up was +3.0 kg/m².

Bilateral adrenalectomy (BA)

Adrenalectomy was performed in 47 patients for Cushing's syndrome (n=28), bilateral pheochromocytoma (n=10) or bilateral adrenal metastases (n=9). Patients in the bilateral adrenalectomy group had the highest median age at diagnosis (50 years) compared to the other two aetiological groups (BA vs AI adjusted P = 0.0013 and BA vs Genetic adjusted P < 0.0001).

Genetic variations

Among this group of 17 patients, the commonest genetic variation was due to variants of *ABCD1* gene (X-linked adrenoleukodystrophy,n=9), followed by *DAX1* mutation (n=3) and

mutation in the *AAAS* gene (triple A syndrome, n=3). One patient had a mutation of *NNT1* gene and one further patient had a mutation of *MRAP* gene responsible for ACTH resistance. This group was the youngest at diagnosis with a median age of 10 years (IQR 6-18; min-max 0-50; adjusted P < 0.0001 for Genetic *vs* AI and *vs* BA), but had the longest duration of follow-up at 21 years.

Glucocorticoid and mineralocorticoid replacement

All patients received glucocorticoid replacement therapy, the vast majority (96%) with hydrocortisone at a mean daily dose of 24.5 ± 7.0 mg, once daily (4%) or divided into two (38.5%), three (56%) or four (1.5%) doses. 35% of patients took more than 25 mg hydrocortisone per day. There were no statistically significant differences in hydrocortisone dose between the three aetiological groups (Table 3). Other glucocorticoid replacement regimens comprised methylprednisolone or dexamethasone alone (n=1 respectively) or a combination of hydrocortisone with dexamethasone or prednisolone (n=3). There was a significant but weak positive correlation between current BMI and hydrocortisone dose (r_s = 0.25, P < 0.0001) and no significant correlation between duration of disease and hydrocortisone dose (r_s = 0.14, P = 0.06).

175 patients (87.5%) also received mineralocorticoid substitution, all with fludrocortisone at a median daily dose of 100 μ g (IQR 50-100). We find a weak negative correlation between age and fludrocortisone dose (r_s = -0.15, *P* = 0.05) but there was no correlation between fludrocortisone dose and the duration of the disease or the BMI. 18% of the total cohort, mostly women (86%), received DHEA at a median dose of 20 mg (IQR 10-25).

Adrenal crisis (AC)

Information regarding AC was available for 89% (n=178) of patients. Of these, 31.5% (n=56) experienced at least one AC over the follow-up period and 9.0% (16/178) experienced more than one crisis (median 1; range 1-6). The incidence of AC was 3.2 per 100 patient-years (89

crises during 2766 years of follow-up in 178 patients for whom information was available). The incidence of AC was significantly associated with a higher disease duration (P = 0.006), but not with sex, age, aetiology or dose of hydrocortisone (either as absolute dose or indexed to body mass) or fludrocortisone (Table 4).

Co-morbidities at last follow-up

Hypertension

Information on blood pressure was available for 160 patients (80%), 27.5% of whom had a diagnosis of hypertension. Bilateral adrenalectomy was the commonest aetiology of PAI among hypertensive patients. There was no association between hypertension and sex, disease duration or hydrocortisone dose. However, the dose of fludrocortisone was significantly lower in hypertensive patients (P = 0.03). Hypertension was significantly related to older age (P = 0.005) and this difference was driven by the subgroup of auto-immune patients (P = 0.002) since there was no association between age and hypertension in either the bilateral adrenalectomy, genetic or other groups (Table 5).

Diabetes

Information about diabetes was available in 162 patients, of whom 22% had a diagnosis of diabetes, corresponding to 17.5% of the total cohort (Table 6). The prevalence in the cohort of type 1 and type 2 diabetes was 8% and 9.5% respectively. Type 1 diabetes was exclusively found in auto-immune patients, with a prevalence of 13% in this group. Individuals with type 2 diabetes had a higher median age than those with type 1 diabetes (69 vs 55 years) but the age difference was not statistically significant (P = 0.16). Type 2 diabetes was significantly associated with higher current BMI (P = 0.0009; adjusted P = 0.0008 type 2 diabetes vs no diabetes), but not with disease duration or dose of hydrocortisone. HbA1c measured at last medical visit was significantly higher in subjects with type 1 than type 2 diabetes (P = 0.005) with a median percentage of 7.9 vs 6.3. There was no correlation between HbA1c and disease

duration ($r_s = -0.07$, P = 0.72) or hydrocortisone dose either per day ($r_s = -0.03$, P = 0.87) or per m² of body surface area ($r_s = -0.08$, P = 0.67).

Osteoporosis

Information on osteoporosis was available for 120 patients (60%) and 101 (50.5%) had a reported DEXA scan (Table 6). 35/120 patients (29%, or 17.5% of the total cohort) had a reported diagnosis of osteoporosis, which was confirmed in 94% by DEXA scanning. Information was not available regarding osteoporotic fractures.

Osteoporosis was more common in females than in males (36% vs 16%; P = 0.02). Postmenopausal status was associated with osteoporosis (88% of women with osteoporosis vs 64% of women without osteoporosis; P = 0.03). Patients with osteoporosis were significantly older (P = 0.0009) and had longer disease duration (P = 0.001) and higher hydrocortisone dose (either as absolute dose P = 0.02 or indexed to body mass P = 0.002) at the time of survey than those without osteoporosis. There was no association between osteoporosis and aetiology of PAI.

Discussion

This study presents data from the first Belgian multi-centre study of patients with PAI. The number of registries in the existing literature is small (Table 1), and furthermore few of these studies pertain specifically to all-cause PAI. German (20) and Scandinavian (8, 17, 21) registries focus more narrowly on auto-immune AI, while conversely the EU-AIR study has broader inclusion criteria also comprising patients with secondary AI (19) who may have a substantially different phenotype. To our knowledge, only four other studies of all-cause PAI of comparable or greater size have previously been published (16, 18, 22, 23) (Table 1).

A novel approach in this study is the categorisation of patients into three major aetiological groups of auto-immune, post-surgical and genetic PAI (we excluded individuals with congenital adrenal hyperplasia). We contend that such categorisation may be clinically useful,

given the heterogeneity our analyses demonstrated between the three groups. Interestingly, the percentage of patients in our study with PAI due to bilateral adrenalectomy (23.5%) was substantially higher than that reported in other studies, which may be due to recruitment bias as some participating centres were specialist referral centres for genetic disease such as von Hippel-Lindau and MEN2, or for oncological disease. The percentage of idiopathic PAI in our study (1%) was low in comparison with other studies which have reported between 3% (22) and as high as 34.9% (18).

The mean daily dose of hydrocortisone in our study $(24.5 \pm 7.0 \text{ mg})$ is at the upper limit of the range recommended by clinical guidelines, but is lower than in Portuguese (26.3 mg) (16) and Swedish (28.1 mg) (21) studies and comparable to EU-AIR (23.4 ± 8.9 mg) (24). Dose of hydrocortisone was not associated with incidence of AC in our study, suggesting that our patients are not undertreated. Of note, in Belgium it is possible to prescribe non-standard doses of medications different from the doses available in commercial preparations, which are then prepared on a named-patient basis by pharmacists. Thus some of our patients were prescribed unusual doses such as 13mg hydrocortisone, which may afford flexibility to reduce the doses taken by patients. 97.5% of our patients were prescribed glucocorticoid therapy with hydrocortisone as per guidelines, which compares favourably with other studies where this figure ranges from 26.5% in Korea (18) to 87% in the EU-AIR study (24).

Our data record an incidence of AC of 3.2 per 100,000 patient years, which is low in comparison with other studies (Portugal 4.36 (16), EU-AIR 6.53 (24), Germany 6.3 (25) or 14-17 (20), Netherlands 5.2 (26)). While we cannot exclude underestimation due to underreporting, in our view this figure reflects two aspects: firstly good access to care in Belgium, which is a geographically small and densely populated country; and secondly a high quality of care of these patients when followed in an academic centre or in a large university-affiliated hospital. Only 31.5% of our patients had experienced one or more AC, which is a

lower percentage than in other studies [EU-AIR 60% (2); Germany 47% (25)]. Thus the majority of patients had relatively stable disease, experiencing a single or infrequent AC, while only a small proportion experience frequent, recurrent crises, as also shown in several previous reports (27, 28). Our finding that glucocorticoid dose is not associated with risk of AC is also corroborated by previous studies (25, 28). Comparability of data may be hampered by lack of a consistent definition of AC in this study and others, particularly given that a significant proportion of patients experiencing AC may not admitted to hospital (25, 27).

A further strength of this study is the availability of data on hypertension, diabetes and osteoporosis, which are rarely examined in other registries (18). However, interpretation of these data is complex given that these conditions may represent either complications of adrenal disease, of glucocorticoid treatment, or incidental co-existent conditions. We note that in our study the incidence of hypertension at 27.5% is consistent with the prevalence expected in the general population, as is the association between hypertension and older age. Patients with hypertension were prescribed lower doses of fludrocortisone, indicating that mineralocorticoid dose was titrated according to blood pressure. While type 1 auto-immune diabetes was more frequently observed, as expected, the prevalence of type 2 diabetes in this adult cohort was also similar to that found in the general population and the disease was not associated with hydrocortisone dose, indicating that it likely represents incidental co-morbidity and should not be ascribed to complications of glucocorticoid treatment.

The prevalence of osteoporosis appears consistent with the findings of previous studies, which demonstrated either mildly reduced (29) or unchanged (30) bone mineral density in patients with PAI compared to the general population. The association in our study between glucocorticoid dose and osteoporosis is also consistent with the published literature (29, 31). Data were insufficient to analyse the relationship between menopausal status and osteoporosis. Of note, prednisolone and dexamethasone (most commonly used in patients

with CAH who were excluded from our study) are associated with lower bone mineral density than hydrocortisone or cortisone (29, 32).

Limitations of this study include the relatively small size, which limits the robustness of statistical analyses. Our case-finding strategy, which depended on voluntary participation by individual clinicians and centres rather than comprehensive enrolment, means that we lacked access to data from a significant proportion of patients with PAI in Belgium and over-represented those followed-up in major Belgian hospitals with experience in the management of PAI. Taking the estimated prevalence of PAI in Europe as 100 per million, we would predict a total of 850 adult patients with PAI in Belgium and thus our survey included only one quarter of all Belgian patients. We note however that a national registry of PAI in Portugal, a country with a comparable population to Belgium, enrolled a similar number of patients (n=278) (16). In our study, patients may have been missed due to the non-participation of one large referral hospital and endocrinologists in the private sector, and non-recruitment of patients with PAI under follow-up in primary care, leading to selection bias. This bias is common to other studies, which predominantly recruit patients through secondary and tertiary care centres, but might result in the underrepresentation of stable, uncomplicated patients who receive care at lower levels of the health care pyramid.

Missing data is a potential challenge in all studies. We noted incomplete or missing data regarding clinical presentation at diagnosis, diagnostic tests, AC and metabolic comorbidities. In particular, we were not able to collect sufficient data to analyse incidence of infections, cardiovascular disease or mortality. However, this level of missing data is comparable to that of other studies (16). Explanations include the complexity of information gathered in the CRF leading to reporter fatigue, and loss of historical data due to the passage of time or change of health care provider, which particularly affects data pertaining to initial diagnosis. The high proportion of patients in our study with iatrogenic PAI due to adrenalectomy may also explain the low numbers of cortisol and ACTH measurements, since the predicted nature of disease onset negates the need for biochemical confirmation of the diagnosis. Despite the antipathic relationship between complexity and accuracy of data collected, it nonetheless remains important to pursue the collection of detailed data in PAI due to the rarity of the condition and limited published data.

In conclusion, this national survey of 200 patients represents the first characterisation of PAI in Belgium and notably provides valuable data on aetiology, co-morbidities, AC and treatment regimens which are indicative of an overall good quality of care. Standardisation of data reported in registries would be invaluable to improve comparability of studies as there is significant variation between studies, such as information collected on laboratory tests and diagnostic workup, co-morbidities, treatment regimens and complications, and even inclusion criteria. Few studies are sufficiently large or have sufficiently broad population coverage to estimate local prevalence of PAI, a question which remains pertinent due to the rarity and geographical variation of the condition. There is also a further need for prospective studies such as EU-AIR (19) to provide robust information about disease and treatment outcomes.

Declaration of interest

We declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Figure legends

Figure 1. Clinical presentation of PAI

Frequency of symptoms and signs at diagnosis (n=128). PAI, primary adrenal insufficoiency; %, percentage ; n, number. **7%**

Table 1. Published studies of Primary Adrenal Insufficiency with ≥ 200 patients

Country	Reference	No. patients/ type of disease	Focus	Key findings pertinent to this study
EU-AIR: Germany, UK, Sweden	3,19,24,28	1054/ PAI and SAI	Ongoing prospective observational study comparing safety and outcomes of different glucocorticoid replacement therapy regimens.	Commonest hydrocortisone dose 20-25 mg/day but significant heterogeneity in treatment regimens Incidence of adrenal crisis 6.53/100 patient years for PAI
Germany	20	1364/ Auto-immune PAI	Epidemiology of auto-immune PAI in database of major health insurance providers	Incidence of adrenal crises 14-17/100 patient years
Sweden	8	1305/ PAI	Analysis of drug prescription patterns in PAI patients from the Swedish National Patient Register vs matched controls	Incidence of PAI 0.5-0.6 per 100,000 person years
Sweden	21	660/ Auto-immune PAI	Prevalence of auto-immune diseases and cardiovascular risk factors in Swedish Addison Registry in Northern Sweden	Mean hydrocortisone dose 28.1 mg/day; association between higher hydrocortisone dose and hypertension
Italy	23	633/ PAI	Clinical and immunological description of a PAI cohort; single centre study at reference hospital	77.7% auto-immune, 9% TB, 4.6% genetic, 1.6% neoplastic, 0.9% post-surgical, 5.1% idiopathic
Italy	22	222/ PAI	Diagnosis and aetiological classification of patients with PAI, national multicentre study	65% with positive antibodies, 13% TB, 3% idiopathic
Norway	17	426/ auto-immune PAI	Clinical and immunological description of national registry of auto-immune PAI	Prevalence of auto-immune PAI 144 per million, incidence 0.44 per 100,000 person years
Portugal	16	278/ PAI	Clinical characteristics, diagnostic workup and treatment of PAI, multicentre study of 12 hospitals	29.1% with inaugural adrenal crisis, incidence of adrenal crises 4.4 per 100,000 patient years: 79% of patients on hydrocortisone, mean dose 26.3 mg/day
Korea	18	269/ PAI	Clinical characteristics, treatment and mortality of PAI, multicentre study of 30 centres	Prevalence of PAI 4.17 per million; incidence 0.45 per million per year; Co-morbidities recorded: hypertension, T2DM and osteoporosis

No, number; PAI, primary adrenal insufficiency; SAI, secondary adrenal insufficiency; mg, milligram; TB, tuberculosis; T2DM, type 2 diabetes mellitus

	Aetiology			
Clinical Characteristics	Auto-immune	Bilateral adrenalectomy	Genetic	<i>P</i> value
	n=125	n=47	n=17	
Sex (F/M)	79/46	35/12	5/12	0.004
Age at diagnosis, y				
median (IQR)	38 (28-45)	50 (28-61)	10 (6-18)	<0.0001
min-max	3-82	16-75	0-50	
Age at survey, y				
median (IQR)	55 (45-70)	56 (42-71)	31 (22-48)	<0.0001
min-max	19-98	22-89	19-70	
Disease duration, y				
median (IQR)	15 (8-28)	9 (5-13)	21 (10-33)	<0.0001
min-max	1-64	1-50	3-40	
BMI at diagnosis, kg/m ² (>18y)				
median (IQR)	21.5 (19.4-24.8)	26.8 (23.9-32.2)	20.1 (17.0-23.5)	<0.0001
min-max (n)	14.5-32.7 (76)	17.1-43.8	17.0-23.5 (3)	
BMI at survey, kg/m ²				
median (IQR)	25.3 (22.2-28.4)	26.2 (23.1-30.7)	22.2 (20.2-28.9)	0.04
min-max (n)	17.3-38.8 (110)	18.4-46.5 (42)	18.1-33.7 (15)	
Δ BMI, kg/m ² (>18y at diagnosis)				
median (IQR)	+3.0 (+0.0 - +6.8)	-0.7 (-2.2 - +1.5)	+2.1 (+0.0 - +4.2)	< 0.0001
min-max (n)	-2.8 - +13.2 (74)	-5.5 - +7.0 (38)	+0.0 - +4.2 (2)	

Table 2. Comparison of clinical characteristics of patients by aetiology of primary adrenal insufficiency (PAI)

F, female; M, male; n, number of subjects; IQR, interquartile ranges between 25th and 75th percentiles; min-max, minimal value-maximal value; Δ BMI, difference between the BMI at diagnosis and at survey. Significant P values are indicated in bold.

Table 3. Glucocorticoid and mineralocorticoid treatment by aetiology of primary adrenal insufficiency (PAI)

	Auto-immune n=125	Bilateral adrenalectomy n=47	Genetic n=17	<i>P</i> value
Daily dose hydrocortisone, mg				
median (IQR)	25 (20-30)	22.5 (17.5-25.0)	22.5 (19.0-27.5)	0.10
min-max	12.5-40 (121)	7-45 (47)	15-45 (17)	
Daily dose hydrocortisone, mg/m ²				
median (IQR)	13.2 (11.1-16.0)	12.1 (10.5-13.2)	13.0 (10.7-15.1)	0.06
min-max (n)	7.3-21.2 (108)	4.5-25.3 (42)	8.1-16.6 (15)	
Daily dose fludrocortisone, µg				
median (IQR)	100 (60-125)	100 (50-112.5)	100 (75-100)	0.58
min-max (n)	25-350 (115)	25-350 (41)	25-150 (13)	

n, number of subjects; mg, milligram; IQR, interquartile ranges between 25th and 75th percentiles; min-max, minimal value - maximal value; µg, microgram.

	Acute adr	.	
Clinical characteristics	Yes (n=56)	No (n=122)	<i>P</i> value
Sex (F/M)	38/18	70/52	0.19
Age, y			
median (IQR)	53 (39-66)	55 (42-70)	0.36
min-max	19-98	20-81	
Disease duration, y			
median (IQR)	15 (9-30)	11 (6-20)	0.006
min-max	2-51	1-45	
Aetiology			
Auto-immune %	64%	60%	
Bilateral adrenalectomy %	21%	28%	0.42
Genetic %	13%	7%	
Other %	2%	5%	
Daily dose hydrocortisone, mg			
median (IQR)	22.5 (20-27.5)	25 (20-30)	0.29
min-max	7.5-40	10-45	
Daily dose hydrocortisone, mg/m ²			
median (IQR)	12.0 (10.9-14.2)	12.8 (10.9-15.4)	0.29
min-max	5.4-19.1	6.3-25.3	
Daily dose fludrocortisone, µg			
median (IQR)	100 (55-100)	100 (50-100)	0.99
min-max	25-350	25-350	

Table 4. Clinical features associated with adrenal crisis

n, number of subjects; F, female; M, male ; y, years ; IQR, interquartile ranges between 25th and 75th percentiles; min-max, minimal value - maximal value; %, percentage; mg, milligram. Significant P value is indicated in bold

	Hypert		
Clinical feature	Yes (n=44)	No (n=116)	P value
Sex, F/M	30/14	74/42	0.60
Age, y median (IQR)	65 (53-74)	55 (43-69)	0.005
Auto-immune, median (IQR), n	72 (63-77), 14	55 (43-69), 83	0.0002
Bilateral adrenalectomy, median (IQR), n	56 (46-72), 25	64 (47-72), 18	0.91
Genetic, median (IQR), n	37, 1	35 (21-50), 8	-
Others, median (IQR), n	74 (61-84), 4	57 (46-74), 7	0.16
Disease duration, y median (IQR)	14 (6-28)	14 (7-27)	0.77
Aetiology	32%	71.5%	
Auto-immune %	57%	15.5%	0.0001
Bilateral adrenalectomy %	2%	7%	
Genetic % Others %	9%	6%	
Daily dose hydrocortisone, mg	22.5 (18-30),	25 (20-30),	0.85
median (IQR), min-max	7.5-45	7-40	
Daily dose hydrocortisone, mg/m ²	12.4 (10.1-16.2),	12.8 (11.0-15.1),	0.62
median (IQR), min-max	5.4-20.8	4.5-25.3	
Daily dose fludrocortisone, µg	69 (50-100)	100 (63-100)	0.03
median (IQR) min-max	25-350	25-300	

Table 5. Clinical features associated with hypertension

n, number of subjects; F, female; M, male ; y, years ; IQR, interquartile ranges between 25th and 75th percentiles; %, percentage; mg, milligram ; min-max, minimal value - maximal value; µg, microgram. Significant P value is indicated in bold

		Diabetes		
Clinical feature	Туре 1 n=16	Type 2 n=19	No diabetes n=127	P value
Age, v				
median (IQR)	55 (47-68)	69 (54-73)	56 (42-70)	
min-max	30-81	45-80	19-98	0.16
Disease duration, y				
median (IQR)	19 (11-30)	11 (5-25)	14 (7-27)	0.52
min-max	4-64	1-45	1-57	
BMI, kg/m ²				
median (IQR),	25.9 (24.6-29.0)	31.6 (26.4-36.1)	25.2 (22.2-29.1)	0.0009
min-max	21.2-38.8	18.7-46.5	17.3-41.0	
Actiology				
Auto-immune %	100%	47.4%	58%	
Bilateral adrenalectomy %	-	47.4%	28%	0.02
Genetic %	-	-	6%	
Other %	-	5.2%	8%	
Daily dose hydrocortisone, mg				
median (IQR)	22.5 (20-30)	25 (21.5-35)	24 (20-30)	
min-max	17.5-35	15-40	7-45	0.14
Daily dose hydrocortisone, mg/m ²				
median (IQR)	12.3 (11.1-15.6)	13.0 (10.7-17.5)	12.4 (10.8-14.9)	0.48
min-max	8.9-17.2	9.1-21.2	4.5-25.3	
HbA1c, %				
median (IQR)	7.9 (6.2-8.6)	6.3 (6.0-6.8)	-	0.005
min-max, n	6.0-9.8, 15	5.5-8.3, 18		

Table 6. Clinical features associated with diabetes

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n, number of subjects; y, years ; IQR, interquartile ranges between 25th and 75th percentiles; min-max, minimal value - maximal value; kg, kilogram; %, percentage; mg, milligram; HbA1c, glycosylated hemoglobin. Significant P value is indicated in bold

	Osteop		
Clinical feature	Yes	No	P value
	(n=35)	(n=85)	
Sex F/M	28/7	49/36	0.02
Age, y			
median (IQR)	67 (52-78)	55 (43-66)	0.0009
min-max	22-89	19-98	
Disease duration, y			
median (IQR)	21 (9-33)	12 (6-24)	0.01
min-max	2-64	1-51	
Aetiology			
Auto-immune %	63%	59%	
Bilateral adrenalectomy %	28.5%	28%	0.49
Genetic %	5.5%	5%	
Other %	3%	8%	
Daily dose hydrocortisone, mg			
median (IQR)	30 (23-30)	24 (20-30)	0.02
min-max	13-45	7-40	
Daily dose hydrocortisone, mg/m ²			
median (IQR)	15.3 (12.3-18.2)	12.4 (11.0-14.2)	0.002
min-max	9.3-25.3	4.5-21.2	

Table 7. Clinical features associated with osteoporosis

n, number of subjects; F, female; M, male; %, percentage; y, years; IQR, interquartile ranges between 25th and 75th percentiles; min-max, minimal value - maximal value; mg, milligram. Significant P value is indicated in bold

1 Figure 1. Clinical presentation of PAI



- 3 Frequency of symptoms and signs at diagnosis (n=128).
- 4 PAI, primary adrenal insufficoiency; %, percentage ; n, number.