RESEARCH

PAI-BEL: a Belgian multicentre survey of primary adrenal insufficiency

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Abstract

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: Two hundred patients were included in this survey. The median age at diagnosis was 38 years (IQR 25–48) with a higher female prevalence (F/M sex ratio = 1.53). The 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 the maintenance dose of hydrocortisone. As high as 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.

Key Words

- primary adrenal insufficiency
- national survey
- glucocorticoid replacement

Endocrine Connections (2023) **12**, **e230044**

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-23-0044

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 the highest case numbers reported in Scandinavian countries (1) and the 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 the 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 μg (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).

Table 1 Published studies of primary adrenal insufficiency with ≥200 patients.

Country	Reference	No. of patients/ type of disease	Focus	Key findings pertinent to this study
EU-AIR: Germany, UK, Sweden	(3, 18, 23, 27)	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	(19)	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	(20)	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	(22)	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	(21)	222/ PAI	Diagnosis and aetiological classification of patients with PAI, national multicentre study	65% with positive antibodies, 13% TB, 3% idiopathic
Norway	(4)	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	(17)	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

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

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https://doi.org/10.1530/EC-23-0044

In recent years, national registries have been reported in European (4, 13, 16) and Asian countries (17). A multinational European prospective registry (EU-AIR) is also underway (18), with the specific aim of determining optimal regimens and safety data for glucocorticoid replacement therapy.

We performed a Belgian survey of PAI (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 PAI.

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 six out of the seven Belgian academic centres and four large university-affiliated hospitals agreed to participate in the data collection. Data collection took place between September 03, 2015, and December 31, 2018. The study was approved by the 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, gastrointestinal symptoms and hyperpigmentation together with at least one of the following criteria: (i) a simultaneous serum level cortisol below and a plasma ACTH 2-fold above reference ranges; (ii) a high plasma ACTH concentration with a failed cortisol response (<400 nmol/L) to 250 µg intravenous ACTH injection and/or (iii) 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 one 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 the 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 S.D. 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 the 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

A total of 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). Twenty-eight 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). The median duration of disease at the time of data collection was 13 years (IQR 7–25, min–max 1–64).

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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%) (Fig. 1). Cutaneous hyperpigmentation was present in 63% and vitiligo in 7%. Fifty-two percent 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/m^2 (IQR 20.1–27.0; min–max 14.5–43.8; $n = 127$).

Diagnostic workup

As high as 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 400 nmol/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. As high as 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 (BA) (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). Fifty-five 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 1 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 commonly associated auto-immune endocrinopathy was thyroiditis (66/115 patients, 57%) on the basis of the presence of auto-antibodies. Sixteen 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 the last follow-up compared to the diagnosis ($P < 0.0001$). The median change over follow-up was +3.0 kg/m^2.

Bilateral adrenalectomy

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 BA 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 the *ABCD1* gene (X-linked adrenoleukodystrophy, $n = 9$), followed by *DAX1* mutation

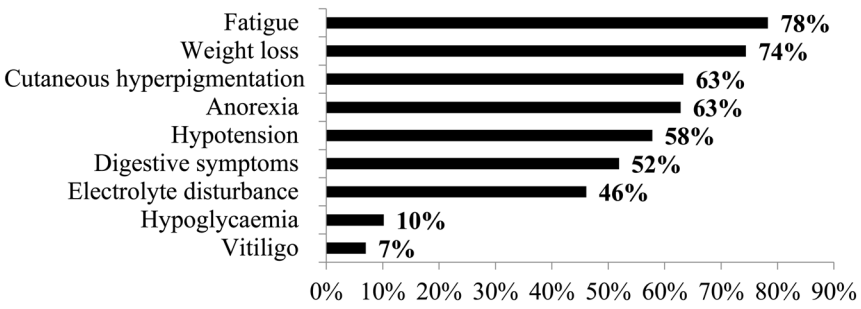

Figure 1
Clinical presentation of PAI. Frequency of symptoms and signs at diagnosis ($n = 128$). *n*, number; %, percentage; PAI, primary adrenal insufficiency.

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https://doi.org/10.1530/EC-23-0044

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

Clinical characteristics	Aetiology			*P* value
	Auto-immune (*n* = 125)	Bilateral adrenalectomy (*n* = 47)	Genetic (*n* = 17)	
Sex (F/M)	79/46	35/12	5/12	**0.004**
Age at diagnosis, years				
median (IQR)	38 (28–45)	50 (28–61)	10 (6–18)	**<0.0001**
min–max	3–82	16–75	0–50	
Age at survey, years				
median (IQR)	55 (45–70)	56 (42–71)	31 (22–48)	**<0.0001**
min–max	19–98	22–89	19–70	
Disease duration, years				
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/m² (>18 years)				
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/m²				
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/m² (>18 years at diagnosis)				
median (IQR)	+3.0 (+0.0 to +6.8)	−0.7 (−2.2 to +1.5)	+2.1 (+0.0 to +4.2)	**<0.0001**
min–max (*n*)	−2.8 to +13.2 (74)	−5.5 to +7.0 (38)	+0.0 to +4.2 (2)	

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

(*n* = 3) and mutation in the *AAAS* gene (triple A syndrome, *n* = 3). One patient had a mutation of the *NNT1* gene and one further patient had a mutation of the *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. As high as 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 a weak positive correlation between current BMI and hydrocortisone dose ($r_s = 0.25$,

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

	Auto-immune (*n* = 125)	Bilateral adrenalectomy (*n* = 47)	Genetic (*n* = 17)	*P* 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/m²				
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)	

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

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https://doi.org/10.1530/EC-23-0044

$P < 0.0001$) and no significant correlation between duration of disease and hydrocortisone dose ($r_s = 0.14$, $P = 0.06$).

A total of 175 patients (87.5%) also received mineralocorticoid substitution, all with fludrocortisone at a median daily dose of 100 µg (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. Of the total cohort, 18%, mostly women (86%), received DHEA at a median dose of 20 mg (IQR 10–25).

Adrenal crisis

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. BA 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 ($P = 0.0002$) since there was no association between age and hypertension in either the BA, 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

Table 4 Clinical features associated with adrenal crisis.

Clinical characteristics	Acute adrenal crisis		*P* value
	Yes ($n = 56$)	No ($n = 122$)	
Sex (F/M)	38/18	70/52	0.19
Age, years			
median (IQR)	53 (39–66)	55 (42–70)	0.36
min–max	19–98	20-81	
Disease duration, years			
median (IQR)	15 (9–30)	11 (6–20)	**0.006**
min–max	2–51	1-45	
Aetiology			
Auto-immune (%)	64	60	0.42
Bilateral adrenalectomy (%)	21	28	
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/m²			
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	

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

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Table 5 Clinical features associated with hypertension.

Clinical feature	Hypertension		
	Yes ($n = 44$)	No ($n = 116$)	*P* value
Sex, F/M	30/14	74/42	0.60
Age, years 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, years			
median (IQR)	14 (6–28)	14 (7–27)	0.77
Aetiology			
Auto-immune (%)	32	71.5	**0.0001**
Bilateral adrenalectomy (%)	57	15.5	
Genetic (%)	2	7	
Others (%)	9	6	
Daily dose hydrocortisone, mg			
median (IQR),	22.5 (18–30),	25 (20–30),	0.85
min–max	7.5–45	7-40	
Daily dose hydrocortisone, mg/m²			
median (IQR),	12.4 (10.1–16.2),	12.8 (11.0–15.1),	0.62
min–max	5.4–20.8	4.5–25.3	
Daily dose fludrocortisone, µg			
median (IQR)	69 (50–100),	100 (63–100),	**0.03**
min–max	25–350	25-300	

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

Table 6 Clinical features associated with diabetes.

Clinical feature	Diabetes			*P* value
	Type 1 (n = 16)	Type 2 (n = 19)	No diabetes (n = 127)	
Age, years				
median (IQR)	55 (47–68)	69 (54–73)	56 (42–70)	0.16
min–max	30–81	45–80	19–98	
Disease duration, years				
median (IQR)	19 (11–30)	11 (5–25)	14 (7–27)	0.52
min–max	4–64	1–45	1–57	
BMI, kg/m²				
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	
Aetiology				
Auto-immune (%)	100	47.4	58	**0.02**
Bilateral adrenalectomy (%)	–	47.4	28	
Genetic (%)	–	–	6	
Other (%)	–	5.2	8	
Daily dose hydrocortisone, mg				
median (IQR)	22.5 (20–30)	25 (21.5–35)	24 (20–30)	0.14
min–max	17.5–35	15–40	7-45	
Daily dose hydrocortisone, mg/m²				
median (IQR)				
min–max	12.3 (11.1–15.6)	13.0 (10.7–17.5)	12.4 (10.8–14.9)	0.48
	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		

Significant *P* values are indicated in bold.
%, percentage; HbA1c, glycosylated haemoglobin; IQR, interquartile ranges between 25th and 75th percentiles; kg, kilogram; mg, milligram; min–max, minimal value–maximal value; *n*, number of subjects.

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(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 the dose of hydrocortisone. Glycosylated haemoglobin (HbA1c) measured at the 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 square metre 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 7). Of 120 patients, 35 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 $=0.002$) at the time of the survey than those without osteoporosis. There was no association between osteoporosis and the aetiology of PAI.

Discussion

This study presents data from the first Belgian multicentre 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 (19) and Scandinavian (4, 8, 20) registries focus more narrowly on auto-immune AI, while conversely, the EU-AIR study has broader inclusion criteria also comprising patients with secondary AI (18) 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, 17, 21, 22) (Table 1).

A novel approach in this study is the categorisation of patients into three major aetiological groups: 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 BA (23.5%)

Table 7 Clinical features associated with osteoporosis

Clinical feature	Osteoporosis		*P* value
	Yes ($n=35$)	No ($n=85$)	
Sex F/M	28/7	49/36	**0.02**
Age, years			
median (IQR)	67 (52–78)	55 (43–66)	**0.0009**
min–max	22–89	19–98	
Disease duration, years			
median (IQR)	21 (9–33)	12 (6–24)	**0.01**
min–max	2–64	1–51	
Aetiology			
Auto-immune (%)	63	59	0.49
Bilateral adrenalectomy (%)	28.5	28	
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/m²			
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	

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

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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 diseases 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% (21) and as high as 34.9% (17).

The mean daily dose of hydrocortisone in our study (24.5 ± 7.0 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) (20) studies and comparable to EU-AIR (23.4 ± 8.9 mg) (23). The dose of hydrocortisone was not associated with the 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 13 mg hydrocortisone, which may afford flexibility to reduce the doses taken by patients. As high as 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 (17) to 87% in the EU-AIR study (23).

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 (23), Germany 6.3 (24) or 14–17 (19), Netherlands 5.2 (25)). While we cannot exclude underestimation due to underreporting, in our view, this figure reflects two aspects: first, 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% (24)). 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 (26, 27). Our finding that glucocorticoid dose is not associated with the risk of AC is also corroborated by previous studies (24, 27). Comparability of data may be hampered by the lack of a consistent definition of AC in this study and others, particularly given that a significant proportion of patients experiencing AC may not be admitted to the hospital (24, 26).

A further strength of this study is the availability of data on hypertension, diabetes and osteoporosis, which are rarely examined in other registries (17). However, the interpretation of these data is complex given that these conditions may represent either complication of adrenal disease, 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 the 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 (28) or unchanged (29) 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 (28, 30). 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 (28, 31).

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

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sector, and the 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.

The missing data are a potential challenge in all studies. We noted incomplete or missing data regarding a clinical presentation at diagnosis, diagnostic tests, AC and metabolic co-morbidities. In particular, we were not able to collect sufficient data to analyse the 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 the 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 the 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 (18) 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.

Funding

This study did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Acknowledgements

The authors are grateful to the Belgian Endocrine Society for assisting with study recruitment. ND and DM are members of the MTG-1 Study Group of the European Reference Network for Rare Endocrine Disease, Endo-ERN.

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Received 5 March 2023
Accepted 10 March 2023
Available online 10 March 2023
Version of Record published 12 May 2023