Clinical, Immunological, and Genetic Features of Autoimmune Primary Adrenal Insufficiency: Observations from a Norwegian Registry

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Objective: Primary adrenal insufficiency [Addison's disease (AD)] is rare, and systematic studies are few, mostly conducted on small patient samples. We aimed to determine the clinical, immunological, and genetic features of a national registry-based cohort.

Design: Patients with AD identified through a nationwide search of diagnosis registries were invited to participate in a survey of clinical features, health-related quality of life (HRQoL), autoantibody assays, and human leukocyte antigen (HLA) class II typing.

Results: Of 664 registered patients, 64% participated in the study. The prevalence of autoimmune or idiopathic AD in Norway was 144 per million, and the incidence was 0.44 per 100,000 per year (1993–2007). Familial disease was reported by 10% and autoimmune comorbidity by 66%. Thyroid disease was most common (47%), followed by type 1 diabetes (12%), vitiligo (11%), vitamin B12 deficiency (10%), and premature ovarian insufficiency (6.6% of women). The mean daily treatment for AD was 40.5 mg cortisone acetate and 0.1 mg fludrocortisone. The mean Short Form 36 vitality scores were significantly diminished from the norm (51 *vs*. 60), especially among those with diabetes. Concomitant thyroid autoimmunity did not lower scores. Anti-21-hydroxylase antibodies were found in 86%. Particularly strong susceptibility for AD was found for the DR3-DQ2/DRB1*0404-DQ8 genotype (odds ratio, 32; $P = 4 \times 10^{-17}$), which predicted early onset.

Conclusions: AD is almost exclusively autoimmune, with high autoimmune comorbidity. Both anti-21-hydroxylase antibodies and HLA class II can be clinically relevant predictors of AD. HRQoL is reduced, especially among diabetes patients, whereas thyroid disease did not have an impact on HRQoL. Treatment modalities that improve HRQoL are needed. **(*J Clin Endocrinol Metab* 94: 4882–4890, 2009)**

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Abbreviations: AADC, Aromatic L-amino acid decarboxylase; APS-I, autoimmune polyendocrine syndrome type I; BP, bodily pain; CI, confidence interval; GH, general health; HLA, human leukocyte antigen; HRQoL, health-related quality of life; MH, mental health; OR, odds ratio; PF, physical functioning; RE, role-emotional; RP, role-physical; SCC, side-chain cleavage enzyme; SF, social functioning; SF-36, Short Form 36; VT, vitality.

Primary adrenal insufficiency (Addison's disease) was a lethal disease until the work of Kendall and Reichstein made glucocorticoid replacement therapy readily available 60 yr ago. Autoimmunity accounts for the majority of cases in industrialized countries (1). Addison's disease is rare, with reported prevalence in European countries at approximately 100 per million inhabitants (2–4), although prevalence is somewhat higher in Scandinavia (140 per million) (5). The rarity of this condition has inevitably resulted in underpowered studies, and only a few have addressed such clinical issues as symptoms, treatment, and procedures for diagnosis and follow-up. No studies have included more than 200 patients (4, 6–11). Significant reduction in subjective health status and working ability among Addison's patients has been found in several populations (10–12), more so in patients with multiple endocrinopathies (10, 12), which affect approximately 50% of patients. Furthermore, an approximately 2-fold increase in all-cause mortality has been found (13, 14), particularly among young males (15). Finally, there is a concern that long-term overtreatment with glucocorticoids may have detrimental effects on bone density (16) and cardiovascular morbidity and mortality (13).

The pathogenesis of autoimmune Addison's disease is still largely unknown, but it is assumed that combinations of genetic and environmental factors are important. However, data on the latter are completely missing. The highest risk is associated with human leukocyte antigen (HLA) DRB1*03-DQA1*05-DQB1*02 (DR3-DQ2) and DRB1*04-DQA1*03-DQB1*0302 (DR4-DQ8), particularly to the genotype DR3-DQ2/DRB1*0404-DQ8, which is quite specific for autoimmune Addison's disease (8, 17). The presence of circulating autoantibodies against 21-hydroxylase, one of the enzymes participating in steroid biosynthesis in the adrenals (18), is the hallmark of the autoimmune form of the disease.

To obtain data on epidemiology, clinical features, and management including health-related quality of life (HRQoL), autoantibodies, and HLA class II associations, we performed a registry-based nationwide survey yielding a large and unbiased sample of 426 patients, the largest cohort published to date. The results provide a framework for improving treatment and identifying individuals at risk to develop Addison's disease.

Patients and Methods

Patients and design

We aimed to identify all adult Addison's patients in Norway who had been registered in an electronic hospital registry. To this end, we searched the in-patient and out-patient registries of all the 57 medical departments in Norwegian hospitals until December 31, 2007. In Norway, the common approach is to refer all patients with suspected or confirmed autoimmune adrenal insufficiency to a consultant endocrinologist in a hospital. We assumed that all Addison's patients had had at least one such contact. In addition, we contacted all endocrinologists working in private health care. The unique personal identification number system in Norway guarantees that every patient was counted only once. Deceased patients were identified in the National Directory of Residents and excluded; they are reported on elsewhere (15). The search criteria were the International Classification of Diseases (ICD) codes 255 (ICD 8 and 9: primary adrenal insufficiency, other adrenal disease) and E27.1-4 (ICD 10: primary adrenal insufficiency, adrenal crisis and other adrenal disease). The codes for adrenal tuberculosis, congenital adrenal disorders, and Waterhouse-Friderichsen syndrome were included, but they identified no patients with Addison's disease. Patients with adrenoleukodystrophy, congenital adrenal hyperplasia, pharmacologically induced adrenal failure, bilateral adrenalectomy, or autoimmune polyendocrine syndrome type I (APS-I; presented in Ref. 19) were excluded.

The medical records of all the patients were scrutinized by endocrinologists for validation of the diagnoses and year of diagnosis. The diagnostic criteria for Addison's disease were one of the following: 1) simultaneous plasma levels of ACTH above and serum cortisol below the reference ranges; 2) a pathological short ACTH-stimulation test (serum cortisol $<$500 nmol/liter); 3) the description of characteristic clinical signs and symptoms such as hyperpigmentation, salt craving, typical electrolyte disturbances, and chronic treatment with glucocorticoids and fludrocortisone. Criterion 3 was only used for a few patients who were diagnosed decades ago. The diagnosis of autoimmune Addison's disease was based on positive autoantibodies against 21-hydroxylase, or the presence of associated autoimmune diseases, or other cases of (non-APS-I) autoimmune Addison's disease in the family. The patients who had no known cause were classified as idiopathic. For quality purposes, the number of patients was compared with figures for prescription of cortisone acetate/hydrocortisone and fludrocortisone from the Norwegian Prescription Database.

All patients were invited to participate in a questionnaire survey and to give blood samples for immunological and genetic analyses. Nonresponders were reminded with a second letter. Each participant completed a registration form covering medical and family history and questions about symptoms, diagnosis, and treatment. The number of patients at ages 18–67 yr receiving disability benefit was recorded and compared with data from the general population provided by the Norwegian Labor and Welfare Service. Subjective health status was assessed with the Short Form 36 (SF-36) (20). Normative data were available (21). Eight scales were calculated: perception of physical functioning (PF), role limitations due to physical problems (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role limitations due to emotional problems (RE), and mental health (MH). The scores range from 0 to 100, and higher scores represent better health.

The Ethical Committee of Western Norway and the Data Inspectorate of Norway approved the study. The study was performed according to the Helsinki Declaration.

Autoantibody assays and genetic analyses

Antibodies against 21-hydroxylase, side-chain cleavage enzyme (SCC), 17-hydroxylase, glutamic acid decarboxylase, ar-

omatic L-amino acid decarboxylase (AADC), and interferon-ω were assayed by methods based on *in vitro* transcription and translation of antigen as described by Oftedal *et al.* (22).

DNA samples were available from 413 unrelated patients with Addison's disease and 684 blood donors. When two or more cases occurred within one family, only one was included in the genetic analyses. DRB1 and DQB1 genotyping was performed with a PCR-based sequence-specific oligonucleotide probe system at four-digit resolution as described elsewhere (23). The DQA1 alleles and HLA-DRB1-DQA1-DQB1 haplotypes were deduced based on known patterns of linkage disequilibrium in the Norwegian population. Exon 3 was not typed, and so we do not distinguish DQB1*0201 from *0202. The *AIRE* gene was sequenced as described by Bøe Wolff *et al.* (24). The transglutaminase IgA-antibody testing was performed with ELISA kit (Generic Assays GmbH, Dalewitz, Germany).

Statistical analyses

SF-36 data are presented as median and interquartile range, and scores in different patient subgroups compared with Mann-Whitney *U* test. *P* values for proportions were calculated using χ^2 analysis. Odds ratios (OR) and *P* values for analyses including HLA data were calculated using logistic regression.

Results

Epidemiology

Applying the diagnostic codes listed above, the initial search in the hospital registries yielded nearly 1000 patients. The diagnostic codes revealed a coding practice that could not alone be trusted to find the patients with primary adrenal insufficiency. The erroneous coding was mostly attributed to suspected cases of Addison's disease not verified by testing, bilateral adrenalectomy, hypopituitarism, and iatrogenic adrenal insufficiency. Ultimately, 664 live subjects with likely autoimmune or idiopathic Addison's disease, including children and patients with APS-I, were identified, yielding a point prevalence of 144 per million inhabitants. When APS-I patients were excluded, the prevalence was 137 per million inhabitants. The group of children with (non-APS-I) autoimmune Addison's disease in Norway comprises five individuals, of whom two are cousins. The estimated incidence rate over the last 15 yr (1993–2007) was 0.44 per 100,000 inhabitants per year. To validate these numbers, data from the Norwegian Prescription Database was retrieved. The prevalence of individuals prescribed cortisone acetate/hydrocortisone and fludrocortisone in combination was 938. Subtracting an estimated 125 patients with salt-wasting congenital adrenal hyperplasia (Nermoen, I., personal communication) and those with bilateral adrenalectomy (10–15% of the patients registered with primary adrenal insufficiency) leaves 690–730 patients with autoimmune or idiopathic Addison's disease in Norway, which is close to our finding of 664.

Patient survey

A total of 426 patients participated in the survey, giving a response rate of 64% [(Geographical distribution shown in Supplemental Fig. S1) (published as supplemental data on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org)]. The sex, age, age at diagnosis, disease duration, self-reported frequencies of concomitant diseases, and occurrences of Addison's disease in family members are given in Table 1 and Supplemental Fig. S2. The nonresponders had a similar mean age (53 yr) but longer disease duration (20 yr), and more males compared with the responders (female:male ratio, 1.14). The majority of the respondents had one concomitant condition, whereas 15 and 8% had two and three, respectively. Autoimmune comorbidity was more frequent in women than in men. Autoimmune thyroid disease, the most commonly associated condition, was found in 47% of the patients. Autoimmune thyroid disease was diagnosed before, at, or after the diagnosis of Addison's disease in about equal numbers of patients (data not shown). Vitiligo was three times more common among males than females, and type 1 diabetes showed a slight male preponderance. We found 27 families with two or more members (first- to third-degree relatives) with Addison's disease, comprising 51 live individuals, of whom all 42 participants in the survey tested negative for *AIRE* mutations.

Replacement therapy

Most of the patients used cortisone acetate because this is the only registered natural glucocorticoid in Norway. The mean dose was 40.5 mg/d (median dose, 37.5 mg); 70% of the patients administered two doses, and 30% used it three times. The replacement doses were similar in patients with isolated Addison's and patients with concomitant autoimmune disease. Of 378 patients who answered questions related to extra doses of glucocorticoids, 28% never took extra doses, 52% took extra doses one to three times a month, and 20% took extra doses more often. The mean fludrocortisone dose was 0.1 mg. Only 5.3% used dehydroepiandrosterone, and all were women.

Diagnosis and follow-up of Addison's disease

Almost 30% of the respondents were diagnosed with Addison's disease within 1 month after presentation of symptoms, whereas 40% were diagnosed after more than 6 months (Supplemental Table S1). The median number of physicians that were consulted before the diagnosis was two (range, 1–20). Sixty-two percent of the respondents were diagnosed during an acute hospital admission. A consultant in endocrinology or internal medicine followed up 80% of the patients; the others were followed by their general practitioners (Supplemental Table S1). Eighty-

TABLE 1. Age, disease duration, self-reported concomitant diseases, and family history of 426 patients with Addison's disease

	Females (n = 273)		Males (n = 153)		Total (n = 426)	
	n	%	n	%	n	%
Mean age (yr)	53 (18–95)[a]		50 (19–90)[a]		53 (18–95)[a]	
Median disease duration (yr)	13 (0–56)[a]		15 (0–52)[a]		14 (0–56)[a]	
Isolated Addison's disease	76	28	89	58	165	39
Associated autoimmune diseases						
Hypothyroidism	139	51	35	23	174	41
Hyperthyroidism	21	7.7	3	2	24	5.7
Type 1 diabetes	26	9.6	23	15	49	12
Premature ovarian insufficiency	18	6.6	NA		NA	
B12 deficiency	32	12	10	6.6	42	10
Autoimmune hepatitis	2	0.7	1	0.7	3	0.7
Vitiligo	16	6	32	21	48	11
Alopecia	12	4.4	4	3	16	3.8
Family history of Addison's disease					41	9.7
Autoantibodies						
21-Hydroxylase autoantibodies	231	86	128	86	359	86
17-Hydroxylase autoantibodies	38	14	8	5.4[b]	46	11
SCC autoantibodies	23	8.7	4	2.7[c]	27	6.5
GAD autoantibodies	62	23	23	16	85	21
AADC autoantibodies	6	2.2	3	2	9	2.2
Transglutaminase IgA-antibodies	11	4.1	5	3.3	16	3.8
Any autoantibody positive	236	89	131	88	367	88

NA, Not applicable; GAD, glutamic acid decarboxylase.

[a] Mean age and disease duration are expressed as number of years (range).

[b] $P = 0.04$, comparison between males and females by χ^2 text.

[c] $P = 0.07$, comparison between males and females by χ^2 test.

eight percent were seen annually or more frequently. Almost all the patients (98%) reported having been given information about increasing glucocorticoid doses during illness and stress.

Symptoms, HRQoL, and working ability

Retrospective self-reported symptoms at diagnosis are given in Table 2. The most frequent symptoms at diagnosis were fatigue, loss of appetite, salt craving, nausea, vomiting, and abdominal pain. Postural dizziness and pain in joints or muscles were also reported by many patients. The most common signs were hyperpigmentation and weight loss, observed in three fourths of patients. Low blood pressure was also common, found in two thirds. The frequencies of all symptoms were sharply reduced after replacement therapy was commenced. Still, 24% reported salt

TABLE 2. Frequencies of self-reported symptoms and signs at diagnosis of Addison's disease and at the time of the survey (on treatment)

	At diagnosis (%)			On treatment (%)		
	Females	Males	Total	Females	Males	Total
Symptoms						
Fatigue	95	95	95	29	15	24
Loss of appetite	72	58	67	4	2.6	3.6
Salt craving	70	52	64	26	21	24
Nausea, vomiting, or abdominal pain	68	52	62	14	2	9.5
Postural dizziness	58	52	56	18	11	15
Muscle or joint pain	45	31	40	25	13	21
Diarrhea	26	19	23	9.6	3.3	7.3
Constipation	14	5.3	10	8.4	1.3	5.9
Signs						
Hyperpigmentation	76	70	74	14	20	16
Weight loss	77	67	73	4.8	2	3.8
Low blood pressure	72	60	68	14	9.3	12
Electrolyte disturbances	38	28	35	4.8	2.6	4
Anemia	15	8.6	13	5.2	1.3	3.8
Vitiligo	8.8	7.9	8.5	7.7	9.9	8.5

craving and 15% postural dizziness with replacement therapy.

The patients' responses to the SF-36 compared with normative data are given in Table 3. VT, GH, SF, and RP were low for all patient categories; the reductions were most pronounced for patients with type 1 diabetes, although not statistically significant. The presence of thyroid disease did not affect the SF-36 scores. The female patients scored worse than healthy females on PF and RP, whereas PF indices in male patients were less affected. MH and BP scores were comparable to the background population.

Thirty percent of the working age patients received full (7%) or part time (23%) disability benefit, compared with 11% (8.5% full, 2.5% partly) in the general population. The percentage of working disability was 19% in patients with isolated Addison's disease and 36% in APS-II. The Addison cohort was slightly older than the reference population, but the increase in working disability was present also in patients in the lower age group less than 40 yr of age. More women than men in the patient population could not explain the increased working disability, which is almost similar in men (9%) and women (12%) in the general population.

Autoimmune etiology

Positive 21-hydroxylase antibodies verified autoimmune etiology in 86% of the patients (Table 1). The proportion of anti-21-hydroxylase-positive patients was significantly lower in those diagnosed before 1980 than after (79 *vs.* 89%; $P = 0.022$; χ^2 test). In 98 patients, at least two samples taken between 1 and 12 yr apart were available for assay of 21-hydroxylase antibodies; four of 93 initial positive patients became negative, whereas one of five initial negative samples reverted to positive. There was no difference in anti-21-hydroylase positivity between sexes, and there was no difference between those with isolated Addison's disease (87%) and those with concomitant autoimmune diseases (85%). More females than males with Addison's disease had antibodies against SCC and 17-hydroxylase. Of 18 females with self-reported premature menopause, 13 had SCC antibodies. Anti-AADC was detected in 2.2%, all of whom were for positive for anti-21-hydroxylase. Because anti-AADC is predominantly found in APS-I patients, anti-interferon ω antibody assay (24, 25) and *AIRE* sequencing were performed, with negative results for all (data not shown). Antibodies indicating untreated celiac disease were found in 16 patients (3.8%); of these, three patients had reported celiac disease. In addition, eight Addison's patients with known celiac disease were not transglutaminase IgA-antibody positive, indicat-

TABLE 3. SF-36 scores of the Addison's patient population and subgroups compared to normative data

	n	PF	RP	BP	GH	VT	SF	RE	MH
Overall									
Patients	417	90 (75–95)	75 (0–100)	84 (52–100)	60 (37–77)	50 (35–70)	88 (75–100)	100 (67–100)	80 (72–92)
Normative	2270	95 (85–100)	100 (75–100)	84 (52–100)	82 (65–97)	60 (50–75)	100 (75–100)	100 (67–100)	84 (84–92)
Females									
Patients	270	85 (65–95)	50 (0–10)	74 (51–100)	57 (35–77)	50 (35–65)	88 (63–100)	100 (67–100)	80 (68–88)
Normative	1184	95 (80–100)	100 (50–100)	80 (51–100)	82 (62–95)	60 (45–70)	100 (75–100)	100 (67–100)	80 (68–88)
Males									
Patients	148	95 (85–100)	100 (25–100)	84 (62–10)	67 (42–82)	60 (40–70)	88 (75–100)	100 (67–100)	84 (72–92)
Normative	1127	95 (85–100)	100 (75–100)	84 (52–100)	82 (65–97)	60 (50–75)	100 (75–100)	100 (67–100)	84 (72–92)
Addison's subgroups									
Isolated Addison's	207	90 (75–100)	75 (10–100)	84 (62–100)	60 (37–77)	55 (35–70)	88 (75–100)	100 (67–100)	80 (68–88)
With AITD only	160	90 (75–95)	75 (0–100)	80 (51–100)	61 (37–79)	50 (35–70)	88 (63–100)	100 (67–100)	84 (72–92)
With DM1 only	22	85 (74–96)	63 (0–100)	84 (51–100)	52 (39–75)	45 (35–70)	75 (63–100)	100 (33–100)	76 (66–88)
With AITD and DM1	28	85 (72–95)	50 (0–100)	79 (51–100)	60 (28–80)	45 (30–68)	75 (50–100)	100 (67–100)	80 (65–91)
With DM1, all	50	85 (74–95)	50 (0–100)	84 (51–100)	57 (34–75)	45 (34–70)	75 (59–100)	100 (67–100)	76 (67–88)

Data are expressed as median (interquartile range). Normative data are from Loge and Kaasa (21). No statistically significant differences were found between the patient subgroups (Mann-Whitney *U* test). AITD, Autoimmune thyroid disease; DM1, diabetes mellitus.

TABLE 4. HLA class II haplotypes in 413 unrelated Norwegian Addison's disease patients and 684 Norwegian controls

			Addison's disease		Controls				
DRB1	DQB1	DQA1[a]	n	%	n	%	OR[b]	95% CI	*P* value
01, 10	0501	0101	32	3.9	145	10.6	0.40	0.23–0.67	0.0006
1401	0503	0101	13	1.6	36	2.6	0.65	0.31–1.35	ns
15	0602, 0611	0102	101	12.2	240	17.5	0.76	0.49–1.17	ns
1301	0603	0103	18	2.2	95	6.9	0.34	0.18–0.64	0.0007
1302	0604	0102	6	0.7	61	4.5	0.18	0.07–0.44	0.0002
07	0201	0201	9	1.1	74	5.4	0.22	0.10–0.48	0.0001
07	0303	0201	14	1.7	34	2.5	0.74	0.36–1.53	ns
0301	0201	0501	284	34.4	188	13.7	2.72	1.81–4.09	2×10^{-6}
04	0301	0301	50	6.1	69	5.0	1.30	0.78–2.18	ns
0401	0302	0301	45	5.4	114	8.3	0.71	0.43–1.17	ns
0404	0302	0301	139	16.8	82	6.0	3.05	1.94–4.81	2×10^{-6}
08	04	0401	30	3.6	60	4.4	0.90	0.51–1.59	ns
11, 12	0301	0501	45	5.4	81	5.9	1 (REF)		
Other[c]			40	4.8	89	6.5			
Total			826	99.9	1368	99.8			

ns, Not significant.

[a] DQA1 are deduced from the DRB1-DQB1 haplotype.

[b] ORs are estimated by logistic regression analysis with the reference haplotype stated as the most equally distributed haplotype in cases *vs.* controls.

[c] The group of other haplotypes contain all haplotypes with a frequency <2% in the controls.

ing adherence to a gluten-free diet. Hence, we found 24 patients (5.6%) with known or probable celiac disease.

In 96% of the patients, we found indications of autoimmune etiology, *i.e.* at least one concomitant organ-specific autoimmune disease, or a family member with autoimmune Addison's disease (APS-I excluded), or at least one positive organ-specific autoantibody. Almost 10% had a relative with Addison's disease (Table 1).

Determination of HLA class II

We confirmed the strong association of Addison's disease to the haplotypes DR3-DQ2 and DR4-DQ8 (Table 4) previously reported in Norwegian patients (8), but now with much stronger statistical power. Moreover, we could confirm that the association with DR4 was confined to the subtype DRB1*0404, whereas DRB1*0401 was not associated with adrenal insufficiency. As shown previously, DQ5 conferred protection, but DRB1*1301-DQB1*0603-DQA1*0103, DRB1*1302-DQB1*0604-DQA1*0102, and DRB1*07-DQB1*0201-DQA1*0201 were also protective. The highest risk for Addison's disease was seen in individuals with the compound heterozygous genotypes DR3-DQ2/DRB1*0404-DQ8 with OR, 32 [95% confidence interval (CI), 14–73] (Table 5). Interestingly, the majority of those with concomitant type 1 diabetes also had DRB1*0404 and not DRB1*0401, which is the common type found in type 1 diabetes, al-

TABLE 5. HLA class II genotypes in 413 unrelated Norwegian Addison's disease patients and 684 Norwegian controls

	Addison's disease		Controls				
DRB1-DQA1-DQB1	n	%	n	%	OR[b]	95% CI	*P* value
*0301-*0501-*0201/*0404-*0301-*0302	96	23.2	7	1.0	32.28	14.36–72.54	4×10^{-17}
*0301-*0501-*0201 homozygous	31	7.5	15	2.2	4.86	2.49–9.49	4×10^{-6}
*0404-*0301-*0302 homozygous	8	1.9	4	0.6	4.71	1.38–16.07	0.013
*0301-*0501-*0201/any other haplotype	126	30.5	151	22.1	1.96	1.38–2.79	0.0002
*0404-*0301-*0302/any other haplotype	27	6.5	67	9.8	0.95	0.57–1.59	ns
Neutral/neutral[a]	82	19.9	193	28.2	1 (REF)		
Neutral/protective[b]	37	9.0	198	28.9	0.44	0.28–0.68	0.0002
Protective/protective[c]	6	1.5	49	7.2	0.29	0.12–0.70	0.006
Total	413	100.0	684	100.0			

ns, Not significant.

[a] DQA1 are deduced from the DRB1-DQB1 haplotype.

[b] ORs are estimated by logistic regression analysis with the reference haplotype stated as the most equally distributed haplotype in cases *vs.* controls.

[c] The group of other haplotypes contain all haplotypes with a frequency <2% in the controls.

though DRB1*0401 was relatively increased in those with concomitant type 1 diabetes (Supplemental Fig. S3). Moreover, the presence of type 1 diabetes was associated with the high-risk genotypes (Supplemental Table S2), as was autoimmune thyroid disease (Supplemental Table S3). Conversely, vitamin B12 deficiency was more frequent among those with low-risk genotypes (Supplemental Table S4). Finally, we found that individuals with this high-risk genotype had lower age of onset (mean age, 28.2 yr) than those carrying neutral or protective genotypes (mean age, 46.1 yr) (Supplemental Table S5). The classification of neutral and protective haplotypes into risk groups is given in Supplemental Table S6.

Discussion

We present here the largest study of Addison's disease published to date. Comprehensive recruitment throughout Norway minimized the selection bias that is often inherent in single-center studies. We found a prevalence of Addison's disease at 144 persons per million inhabitants, which is close to that found in Western Norway in 2000 (5). The incidence rate of 0.44 per 100,000 inhabitants per year was somewhat lower than that found previously (5). The current prevalence figure is not likely to be an overestimation because the diagnosis was validated by scrutiny of the medical records. Rather, an underestimation can be inferred because death in Addison crisis is known to occur before the diagnosis is made.

The female to male ratio in the survey was 1.8, which is comparable to our earlier report (8) and to those from Italy (2), the United Kingdom (3, 4), and Denmark (6). Addison's disease rarely presented before 10 yr of age, and when diagnosed in childhood it is usually part of APS-I (19, 26) or adrenoleukodystrophy (27). The oldest patient in the survey was 86 yr old at diagnosis, and 64 patients were diagnosed after 50 yr of age. Less sex difference was seen in patients younger than 30 yr of age, which is similar to the sex distribution in type 1 diabetes (28).

We demonstrated autoimmune etiology in 96% of the patients. Consequently, in clinical practice, if anti-21-hydroxylase antibodies are detected, further investigation of the etiology is unnecessary. Almost two thirds reported associated autoimmune diseases, confirming earlier reports in smaller patient samples (6, 8). The high frequency of autoimmune thyroid disease warrants annual screening of thyroid function tests and thyroperoxidase antibodies because clinical symptoms of hypothyroidism may be mild and may be misinterpreted as symptoms of Addison's disease. Moreover, vitamin B12 deficiency can be difficult to detect clinically, and screening in Addison's patients is warranted. SCC antibodies were predominantly found in women, and the presence was associated with premature ovarian insufficiency (29, 30). SCC antibodies could thus be used as an indicator of premature ovarian insufficiency, and their presence should alert women not to postpone desired pregnancies.

Our large patient and control samples have estimated HLA class II risk with greater accuracy than earlier studies. The major risk genotype was the compound heterozygote combination of DR3-DQ2 and DR4-DQ8 with OR of 32 (8, 17). A correlation between risk genotype and age at diagnosis was evident; the higher the genetic HLA risk, the earlier the disease presents. This suggests that determination of HLA class II genotype should be included in the assessment of patients with 21-hydroxlase antibodies (31). Such assessment will be particularly valuable if early intervention therapy becomes available that could halt the autoimmune destruction of the adrenal cortex.

Our survey shows that about half of the patients were diagnosed within 6 months from symptom presentation. This is a shorter period than what most textbooks and reviews describe, which may reflect increased awareness of the disease among patients and physicians. However, 64% of the patients were diagnosed only after an acute hospital admission. Many participants reported extreme weakness and the feeling of being severely ill before the diagnosis was made; some were unconscious with a life-threatening condition. In a recent study of mortality in Addison's disease, we found indications that deaths due to undiagnosed Addison's disease and acute adrenal crises remain a problem (15). Many of the symptoms and signs are unspecific, but at the time of diagnosis hyperpigmentation was reported by 74% of the patients, hypotension by 64%, and salt craving by 68%. These are quite specific signs and should alert the physician to the possibility of Addison's disease. Salt craving as a symptom is not sufficiently appreciated in medical textbooks, which report frequencies of 12–19%. It is our experience that the patients withhold information of this clinical feature unless specifically asked about it. Improved physician education and the use of early markers of autoimmune adrenal failure such as 21-hydroxylase antibodies should facilitate earlier diagnosis before the onset of a life-threatening adrenal crisis.

Two thirds of the patients regularly consulted an endocrinologist or internist, most often at the local hospital. Expert follow-up is important to obtain the optimal replacement therapy and to provide surveillance for other autoimmune manifestations. Reassuringly, almost all patients acknowledged that they had received information about stress doses. An indication of a possible chronic underreplacement of fludrocortisone is the persistent salt craving and postural dizziness reported by treated pa-

tients, which may make the patient more prone to cardiovascular collapse. On the other hand, despite expert follow-up, the majority of the patients still use higher than recommended doses of glucocorticoids based on endogenous production (31, 32). This may have detrimental metabolic long-term effects (16) and may increase insulin resistance (33). Indeed, one study found increased cardiovascular mortality (13), whereas we did not find this association (15). Novel parameters of glucocorticoid action are needed to optimize dosing (16).

Previous studies in Norway (12), Germany (9, 10), and the United Kingdom (11) have reproducibly shown impaired HRQoL in patients with Addison's disease, particularly reduced vitality and general health perception, and reduced physical functioning in women. The current study corroborates and extends these previous observations. Vitality perception was impaired in all subgroups of patients, indicating that reduced energy is a true feature of adrenal insufficiency. Conversely, patients with conventional replacement therapy report normal or less pain compared with the general population, perhaps reflecting overreplacement of glucocorticoids. The ideal treatment with glucocorticoids is probably a combination of timely distributed doses adjusted to the diurnal needs of the individual. Weight-related dosing (34), timed curves of salivary cortisol (35), and a systematic clinical evaluation (36) should enable many patients to reduce their daily doses. Recent developments of more physiological glucocorticoid replacement therapies such as modified-release hydrocortisone tablets (37) and continuous sc hydrocortisone infusion (38) might improve HRQoL and reduce adverse effects.

In conclusion, Addison's disease in Norway is mainly autoimmune, and the clustering in families is the greatest reported so far. The dominant risk genotype was the combination DR3-DQ2 and DR4-DQ8, which predicts early disease. Both 21-hydroxylase and HLA-class II genotyping should be clinically useful markers to predict Addison's disease in risk populations. The diagnosis is delayed in many cases, and the care of patients must include diagnostic awareness for other autoimmune diseases. Our findings indicate that patients are overreplaced with glucocorticoids. Whether nonphysiological glucocorticoid replacement or underreplacement of fludrocortisone is connected to reduced HRQoL is not known and requires further studies.

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