Delayed Diagnosis of Adrenal Insufficiency Is Common: A Cross-Sectional Study in 216 Patients

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Abstract: *Introduction:* Little information is available on patients with adrenal insufficiency (AI) in regard to complaints before diagnosis, time until correct diagnosis, false diagnosis, and professional changes due to the diagnosis. *Objective:* We retrospectively evaluated circumstances before and at diagnosis of AI in patients with primary and secondary AI by using established Hospital Anxiety and Depression Scale, Short Form-36 and Giessen Complaint List (GBB-24) questionnaires, and a self-established general registration form. *Methods:* In this cross-sectional study, questionnaire sets were available from 216 patients (primary AI, n = 99; secondary AI, n = 117). Time duration before treatment, underlying diagnoses, and disease symptoms were verified by questionnaires and review of medical records. Results regarding subjective health status (SHS) were compared with sex- and age-matched controls drawn from questionnaire-specific reference cohorts. *Results:* Less than 30% of woman and 50% of men with AI were diagnosed within the first 6 months after onset of symptoms. Twenty percent of patients suffered >5 years before being diagnosed. More than 67% of patients consulted at least 3 physicians, and 68% were primarily false diagnosed. The most common false diagnoses were of psychiatric and gastrointestinal origin. Overall, patients with AI showed an impaired SHS compared with controls, and patients who were diagnosed correctly within 3 months showed a significantly better SHS. *Conclusions:* Because of the unspecific symptoms, diagnosis is often delayed, not recognized by physicians or diagnosed falsely. An early diagnosis is necessary and might positively influence SHS in patients with AI.

Key Indexing Terms: Quality of life; Primary and secondary adrenal insufficiency; Symptoms. **[Am J Med Sci 2010;339(6):525–531.]**

Adrenal insufficiency (AI) may result either from a loss of function of the adrenal gland itself [primary AI, (PAI)] or by an insufficient secretion of adrenocorticotropic hormone or corticotropin-releasing hormone in the hypothalamic-pituitary region [secondary AI, (SAI)].[1] Nowadays, in PAI, 80% to 90% of the patients suffer from autoimmune adrenalitis, whereas the main cause of SAI is the growth or the result of treatment of a tumor in the pituitary region often leading to panhypopituitarism.[1–3] Because of the long-term lack of cortisol production, patients with PAI and SAI rely on a lifelong, daily medical treatment with glucocorticoids. Patients with PAI need an additional treatment with mineralocorticoids.[1] Patients with SAI often depend on additional hormonal treatment because of insufficiency of further pituitary hormonal axis. Before medical drugs were available, the majority of patients died within few years after diagnosis.[4] Because AI became treatable with glucocorticoids, patient's life expectancy has improved significantly. Although patient's health status has increased, recent studies demonstrated still a significantly impaired quality of life irrespective of age, sex, concomitant disease, used glucocorticoids, and primary or secondary origin of AI compared with the normal population.[5–8]

In most cases, symptoms of AI develop slowly over a longer time period. The clinical features are mostly nonspecific, thus often leading to delay of diagnosis and treatment, misdiagnosis and invasive workup, particularly in previously unknown adrenal disease.

The aim of our current cross-sectional, retrospective study was to investigate the complaints before diagnosis of AI, the time from onset of symptoms until diagnosis, and the circumstances of diagnosis. In addition, we were interested in the subjective health status (SHS) in our patients with PAI and SAI.

METHODS

Subjects

Data collection was performed within a German Survey of patients with PAI and SAI.[6–8] All patients with AI are currently registered in the outpatient clinic of the endocrine department of the Charité Campus Mitte Berlin and private endocrine practices in Berlin (n = 535). Most of the patients seen in the endocrine department are from the region East Berlin and federal state Brandenburg. Patients from West Berlin are mostly seen in private practices that participated in this survey. All patients were recruited between April and December 2006. The patients were asked to participate in a postal survey. The study was approved by the ethical committee of the Charité Campus Mitte Berlin (permit no. ES1/037/06), and written informed consent was obtained from all patients before participation. The study was conducted in accordance with the guiding principles for human experimentation summarized in the latest version of the Helsinki Declaration. Participating patients received the questionnaires, which they had to complete without consulting friends or family members, and were asked to return the completed questionnaires.

The underlying diagnosis of AI was verified by review of the medical records. In addition, the following exclusion criteria were applied: AI due to long-term pharmacologic glucocorticoid treatment, glucocorticoid doses >7.5 mg prednisolone equivalent for other reasons than AI, adrenocortical carcinoma, congenital adrenal hyperplasia, adrenoleukodystrophy, and patients with <12 months duration of disease or who received drugs causing AI.

Questionnaires

Patients were asked to complete 3 different questionnaires and 1 self-established general registration form. Psychometric evaluation of patients was performed using 3 validated self-assessment SHS questionnaires: the Short

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TABLE 1. Clinical data of patients with primary and secondary adrenal insufficiency

	Age (yr)	Duration of disease (yr)	BMI (kg/m^2)
Total (n = 216)	54 ± 16 (57; 18–84)	14 ± 11 (12; 1–57)	25.8 ± 4.3 (25.3; 16.6–39.6)
PAI (n = 99)	51 ± 15 (48; 20–84)	14 ± 11 (12; 1–45)	24.7 ± 3.7 (23.9; 18.7–36.4)
SAI (n = 117)	57 ± 16 (62; 18–81)	15 ± 11 (13; 1–57)	26.8 ± 4.6 (26.5; 16.6–39.6)
Men (n = 82)	56 ± 16 (56; 23–84)	13 ± 9 (10; 1–41)	26.6 ± 3.7 (26.2; 16.6–37.6)
Women (n = 134)	53 ± 16 (54; 18–81)	16 ± 11 (14; 1–57)	25.3 ± 4.6 (24.1; 18.7–39.6)

Data are shown as mean ± SD (median; range).
BMI, body mass index; PAI, primary adrenal insufficiency; SAI, secondary adrenal insufficiency.

Form-36,[9–12] the brief form of the Giessen Complaint List (GBB-24),[13] and the Hospital Anxiety and Depression Scale.[14–16] All 3 questionnaires are presented as a self-explanatory, multiple-choice self-assessment. A self-established general registration form collected data specifically matched for this survey. The questionnaire contained multiple-choice questions and space for free text. We were especially interested in issues in regard to time until diagnosis, false diagnosis, complaints before diagnosis, and professional changes. In addition, data were collected on duration and cause of AI, medication, and additional endocrine and general health problems.

Patients were grouped according to their sex and PAI and SAI. In a subgroup analysis, patients with pituitary surgery or bilateral adrenalectomy were excluded, and we compared patients with different durations of complaints before diagnosis with regard to the subjective quality of life. The results of the 3 standardized questionnaires between the groups were also analyzed.

Statistical Analysis

Comparison of quality-of-life scores between patients and matched controls was performed by Mann-Whitney *U* test. Before comparison of the subgroups of patients with PAI and SAI, which were inhomogeneous regarding age and sex distribution, adjustment for age and sex was performed by transformation of score values from patients and controls into age- (decade) and sex-adjusted *Z* scores. Calculation of *Z* scores was based on the complete data set from the respective normative groups. Differences in *Z* scores, age, and BMI were subsequently analyzed by Mann-Whitney *U* test. In addition, significance of differences was determined by unpaired *t* test or χ^2 test when appropriate.

Analyses were performed using the statistical software package SPSS, version 15.0 (SPSS Inc, Chicago, IL). A *P* value <0.05 was considered statistically significant.

RESULTS

Cohort Description

Five hundred thirty-five patients with AI were contacted by mail, 270 patients agreed to participate and signed the consent form. Fifty-four patient's datasets were filled out inappropriately and had to be excluded. Finally, 216 questionnaires were considered for further analysis. Ninety-nine of the 216 patients suffered from PAI (46%) and 117 from SAI (54%). Thirty-eight percent of the participants were males (n = 82) and 62% were females (n = 134). Table 1 presents clinical data of our patient cohort.

Sixty-five patients (66%) with PAI suffered from autoimmune adrenalitis, and 54 patients (55%) of those developed autoimmune polyglandular syndrome type 2. Twenty-seven percent were bilaterally adrenalectomized; tuberculosis was diagnosed in 4% of the cases. Further 2% had other or unknown reasons for their PAI. Pituitary adenoma was responsible for 62% of the cases with SAI. Twenty percent of patients with SAI had other tumors or cysts. Ten percent of all female patients with SAI had postpartal Sheehan syndrome. Other sources of SAI, such as the empty sella syndrome, or traumatic reasons were stated in 13%.

Time Until Diagnosis and False Diagnosis

Regarding evaluation of the time until diagnosis and false diagnosis, we excluded patients with bilateral adrenalectomy or pituitary surgery, with infectious or malignant disease, and performed a subgroup analysis of the nonoperated patients. Within this subgroup, 47% of patients with AI were diagnosed within the first year of onset of symptoms. However, 20% of the patients suffered >5 years before being diagnosed. Compared with men, women were diagnosed significantly later (Figure 1). This was observed in both patients with PAI and SAI.

Only in 15% of all AI cases, the first physician gave the correct diagnosis (Figure 2). The majority of patients (67%) consulted at least 3 physicians; almost every third patient (30%) visited 5 or more different doctors before AI was diagnosed. More than two-thirds of the patients (68%) were primarily false diagnosed (Table 2). Psychotic or psychiatric causes were given in almost every second patient (41%). Especially, women and patients with PAI had significantly more often been falsely diagnosed.

Symptoms and Complaints at Diagnosis

The most common symptoms in patients with AI, regardless of AI cause, were fatigue and lack of energy (Table 3). However, there were significant differences between patients with PAI and SAI in regard to symptoms and complaints and between the sexes (Table 3). For example, while in PAI more than every second woman suffered from nausea and vomiting, only 25% of men with PAI displayed these symptoms ($P < 0.001$ and $P < 0.005$, respectively). A loss of axillary and pubic hair was noticed in every third women with PAI but only in 3% of men with PAI ($P < 0.001$). Furthermore, fatigue, loss of weight, hypotension, loss of appetite, nausea, vomiting, stomach pain, and diarrhea were significantly more often seen in PAI than in SAI (Table 3). As expected, loss of axillary and pubic hair ($P < 0.005$) and pale skin ($P < 0.001$) were significantly more often observed in SAI than in PAI.

Present Patient's SHS and Occupational Changes

Under the current replacement therapy, the most common symptoms and complaints of patients with AI were dry

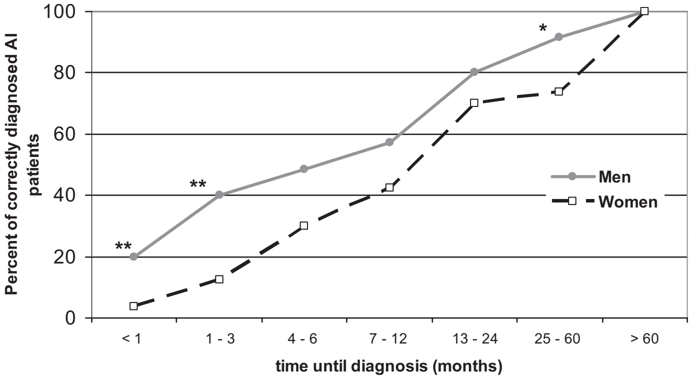

FIGURE 1. Percent of correctly diagnosed patients with adrenal insufficiency (AI) depending on the time between onset of symptoms and complaints and correct diagnosis of AI. Subgroup analysis of nonoperated patients. **$P < 0.005$, ***$P < 0.001$ compared with women.

skin, a lack of concentration, loss or impairment of libido, cold hands and feet, and difficulties of getting out of bed in the morning (Table 4). Patients with SAI complained significantly ($P < 0.05$) more often about gaining weight, whereas patients with PAI mentioned significantly ($P < 0.005$) more often weight loss. Among patients with PAI and SAI, several symptoms and complaints were different between the sexes (Table 4). Although patients with AI think to cope well with their disease, they evaluated their own physical condition neither good nor bad (Figure 3).

Interestingly, patients who were diagnosed correctly within 3 months after the onset of their complaints had significantly lower anxiety scores (Figure 4A). These patients complained significantly less about gastric and heart symptoms and mentioned less often pain in the limbs and exhaustion tendencies (Figure 4B). In the Short Form-36 questionnaire, a similar trend was seen; however, it reached significant levels only in 1 of 8 dimensions: mental health, with less complaints in early diagnosed patients (Figure 4C).

Surprisingly, in more than one-third of our cases, the professional situation changed because of the diagnosis of AI. Every fourth patient became even incapable to work leading to early retirement and receiving pensions (Table 5).

During follow-up, >90% of our patients with AI were seen at least twice a year by their physician. About 10% of patients with AI had a no-glucocorticoid emergency card, and only 20% of men with AI and 33% of women with AI also owned an emergency kit.

DISCUSSION

We investigated a large cohort of patients with PAI and SAI in regard to their SHS. Many of our patients suffered a long time from the onset of symptoms until diagnosis. In every second patient, AI was diagnosed after >1 year of complaints and confirms recent data from Arlt.[2] Especially, women were often diagnosed at a later time point than men. Similar differences between women and men were described for acute coronary syndromes.[17] A possible explanation might be that women have higher pain experience levels than men[18,19] and that gender differences in the experience of pain may arise from differences in the experience and processing of emotion that, in turn, differentially alter pain processing.[20] However, symptoms in women seemed to be taken less seriously by physicians than symptoms in men.

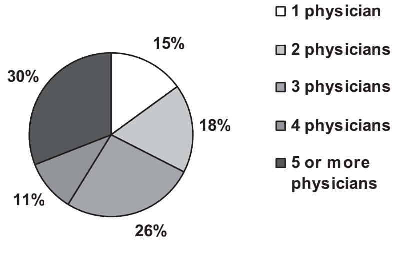

FIGURE 2. Number of different physicians seen by patients with adrenal insufficiency (AI) because of her/his symptoms and complaints before the correct diagnosis was given. Subgroup analysis of nonoperated patients.

The time lag in diagnosis may be explained by the fact that AI often develops slowly over months that patients may not notice physical changes in the beginning unless the patient suffers from an acute adrenal crisis.[21] In addition, most symptoms are unspecific and are not directly leading to the diagnosis of AI. Therefore, diagnosing AI is still difficult.[22–24] This is emphasized by the finding in our study that <50% of patients with AI were diagnosed within a year. A comparable, but not peer-reviewed, study was performed in North America and published by the National Adrenal Diseases Foundation in 1997 (North American Survey; available at: www.nadf.us/news/survey1997.htm). In the survey of patients with PAI, more than 63% of the patients were diagnosed within a year. This difference implies that medical students and young doctors in Germany need to be better trained, especially in the field of endocrinology. Secondly, a greater ease of specialty referral is needed in Germany.

Fatigue and loss of energy were mentioned most often as well as unspecific symptoms such as weight loss, a loss of appetite, vomiting, and nausea. These unspecific symptoms and complaints led often to the false diagnosis of psychiatric or gastrointestinal diseases. The more specific PAI symptoms such as hypotension (55%), hyperpigmentation of patient's skin (41%), and salt craving (38%) were less often present in our study cohort. This is in contrast to other studies showing higher percentage of hypotension (80%) and hyperpigmentation (90%),[25,26] but salt craving (15%) was reported to a lesser extend.[23,24] Fatigue, loss of libido, loss of axillary and pubic hair, headaches, and pale skin were symptoms reported in our patients with SAI and confirmed previous reports.[1,3,4,26]

Anglin et al[27] noticed that neuropsychiatric symptoms such as misconception, depression, and emotional or affective disorders are likely to be often underestimated signs of patients with AI, leading to wrong diagnosis or to no diagnosis at all. This may explain partly our finding that every third patient in our cohort consulted 5 or more physicians before AI was

TABLE 2. False diagnosis (in percent) in a subgroup of nonoperated patients with PAI and SAI

	False diagnosis (total)	Psychotic and psychiatric diseases	Gastrointestinal diseases	Others (eg, cardiovascular diseases and tumors)
Total (n = 118)	68%	41%	21%	46%
PAI (n = 74)	82%	50%	31%	54%
SAI (n = 44)	45%	27%	5%	32%
P (PAI vs. SAI)	<0.001	<0.05	<0.005	<0.05
Men (n = 48)	46%	16%	13%	29%
Women (n = 70)	79%	53%	25%	54%
P (men vs. women)	<0.001	<0.001	NS	<0.05

The sum of false diagnosis is not 100% because of several false-diagnosed events by different doctors.
PAI, primary adrenal insufficiency; SAI, secondary adrenal insufficiency; NS, no significance.

diagnosed. In women with AI, it was even nearly every second one, and about 85% of all our patients with AI consulted more than 1 physician with their complaints, which is similar to the data from the North American Survey (available at: www.nadf.us/news/survey1997.htm). The high number of consulted physicians, the constant misdiagnosis by medical staff, and the persistent complaints may lead to a chronification of symptoms. It may be possible that a delayed diagnosis of AI influences patient's health-related quality of life seen in our study. The quality of life of patients who were untreated for >3 months was significantly impaired compared with early diagnosed (<3 months) patients. Lately diagnosed patients were more often exhausted, complained significantly more often about gastric symptoms and heart complaints, and mentioned more rheumatic pain. Furthermore, those patients suffered more from anxiety. In addition, one might hypothesize that long-term lack of glucocorticoids might lead to a possible chronification of complaints. Effects of glucocorticoids on the central nervous system and chronic changes in their secretion pattern might explain altered cognitive function and anxiety. However, even if AI was diagnosed at an early stage, AI patient's SHS was still significantly impaired compared with controls. This emphasizes that the current hormone substitution therapy is not ideal and new treatment regimens are necessary. Whether suggested premature mortality in AI[28,29] might be reduced in early diagnosed and treated patients with AI is still unknown.

Changes in quality of life, complaints and symptoms of patients with AI influence also patient's profession. In one-third of our patients with AI, professional chances were reported and were of major concern. Every fourth patient even had to quit his/her job because of incapability of work and had led to early retirement. This is higher than the recently published data by Hahner et al.[7] The overall quota of being out of work and receiving disability pensions in the general German population was 4.1% and therefore 6 times lower than in patients with AI. In the North American Survey (available at: www.nadf.us/news/survey1997.htm), 17.2% of the patients with PAI were retired and 13.3% were unable to work, leaving only 69% of

TABLE 3. Symptoms and complaints of patients with PAI and SAI at the time of correct diagnosis (in percent)

	Total (n = 216)	PAI (n = 99)	PAI Men (n = 32)	PAI Women (n = 67)	*P* (PAI Men vs. Women)	SAI (n = 117)	SAI Men (n = 50)	SAI Women (n = 67)	*P* (SAI Men vs. Women)	*P* (PAI vs. SAI)
Fatigue/lack of energy	73%	84%	74%	88%	NS	64%	53%	71%	<0.05	<0.005
Loss of weight	47%	66%	55%	72%	NS	30%	21%	38%	NS	<0.001
Loss of libido	43%	39%	32%	42%	NS	47%	46%	48%	NS	NS
Hypotension	43%	55%	45%	60%	NS	32%	21%	41%	<0.05	<0.001
Loss of appetite	40%	53%	39%	60%	NS	29%	17%	38%	<0.05	<0.001
Headaches	39%	32%	19%	37%	NS	45%	31%	55%	<0.05	NS
Nausea	36%	49%	23%	61%	<0.001	24%	15%	31%	<0.05	<0.001
Dry skin	35%	34%	19%	40%	<0.05	37%	17%	52%	<0.001	NS
Loss of axillary and pubic hair	35%	24%	3%	34%	<0.001	45%	31%	55%	<0.05	<0.005
Pain in the limbs	31%	36%	26%	40%	NS	28%	19%	34%	NS	NS
Vomiting	31%	44%	23%	54%	<0.005	21%	15%	25%	NS	<0.001
Pale skin	27%	15%	10%	18%	NS	37%	19%	50%	<0.001	<0.001
Hyperpigmentation	21%	41%	32%	45%	NS					
Salt craving	18%	38%	19%	46%	<0.05					
Stomach pain	14%	23%	19%	25%	NS	5%	4%	6%	NS	<0.001
Diarrhea	14%	23%	13%	28%	NS	6%	4%	8%	NS	<0.001

PAI, primary adrenal insufficiency; SAI, secondary adrenal insufficiency; NS, no significance.

TABLE 4. Most common symptoms and complaints under present treatment in patients with PAI and SAI

	Total (n = 216)	**PAI (n = 99)**	**PAI Men (n = 32)**	**PAI Women (n = 67)**	***P* (PAI Men vs. Women)**	**SAI (n = 117)**	**SAI Men (n = 50)**	**SAI Women (n = 67)**	***P* (SAI Men vs. Women)**	***P* (PAI vs. SAI)**
Dry skin	71%	70%	53%	78%	<0.05	73%	64%	79%	NS	NS
Lack of concentration	68%	68%	56%	73%	NS	68%	68%	67%	NS	NS
Reduced libido	67%	63%	47%	70%	<0.05	70%	72%	69%	NS	NS
Cold hands and feet	66%	63%	59%	64%	NS	69%	64%	73%	NS	NS
Tendency of gaining	64%	57%	56%	57%	NS	70%	60%	78%	<0.05	<0.05
Difficulties in getting out of the bed	56%	64%	56%	67%	NS	50%	42%	55%	NS	<0.05
Sleeplessness	55%	55%	34%	64%	<0.05	56%	48%	61%	NS	NS
Headaches	55%	57%	44%	63%	NS	53%	46%	58%	NS	NS
Extreme thirst	52%	46%	28%	55%	<0.05	56%	52%	60%	NS	NS
Muscle weakness	46%	46%	41%	49%	NS	45%	40%	49%	NS	NS
Hypersensitivity in coldness	45%	42%	28%	49%	<0.05	48%	36%	57%	<0.05	NS
Dry eyes	45%	44%	25%	54%	<0.05	45%	44%	46%	NS	NS
Alopecia	43%	44%	25%	54%	<0.05	42%	26%	54%	<0.005	NS
Muscle cramps	40%	38%	41%	37%	NS	41%	42%	40%	NS	NS
Hypersensitivity in warmth	39%	41%	31%	46%	NS	38%	22%	49%	<0.005	NS
Salt craving	32%	51%	38%	57%	NS	16%	18%	15%	NS	<0.001
Diarrhea	31%	29%	22%	33%	NS	32%	40%	27%	NS	NS
Obstipation	23%	21%	9%	27%	<0.05	25%	20%	28%	NS	NS
Loss of appetite	20%	20%	13%	24%	NS	20%	8%	28%	<0.05	NS
Tendency of loosing weight	16%	24%	19%	27%	NS	9%	8%	10%	NS	<0.005
Vomiting	15%	18%	13%	21%	NS	13%	8%	16%	NS	NS
Hearing loss	14%	12%	13%	12%	NS	15%	12%	18%	NS	NS

PAI, primary adrenal insufficiency; SAI, secondary adrenal insufficiency; NS, no significance.

patients with PAI still working. In this survey also, 52% of patients stated that they had experienced difficulties in their social or financial life because of their disease. The disease-caused change of profession or even of job retirement may lead to a further stigmatisation and possible chronification of reduced quality of life.

In contrast to patients with diabetes mellitus, patient education in AI is not yet well structured regarding prevention and handling of adrenal crisis. Although the majority of our patients carried an emergency card, only a small percentage of patients had been provided with an emergency glucocorticoid set for intravenous administration. This highlights the need for a better education of patients with AI and of family members, including training in the use of emergency glucocorticoids.

It is necessary to point out that our study has several limitations: First, it is a retrospective investigation in patients suffering from adrenal disease for up to 57 years. Thus, it might have been difficult to exactly remember the complaints and circumstances before diagnosis of AI and the exact numbers of

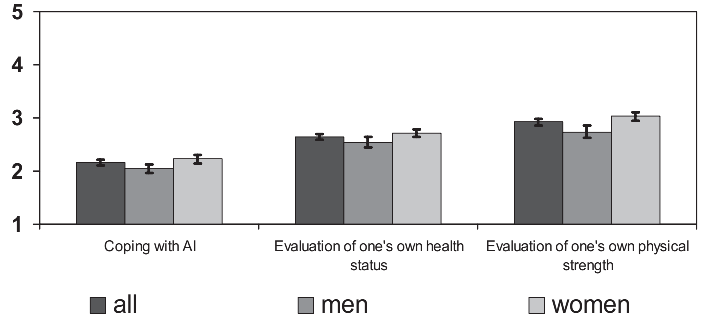

FIGURE 3. Self-assessment regarding perception of their disease in patients with adrenal insufficiency (AI). The patients had to rate themselves between 1 and 5. 1, very good; 2, good; 3, neither good nor bad; 4, bad; 5, very bad.

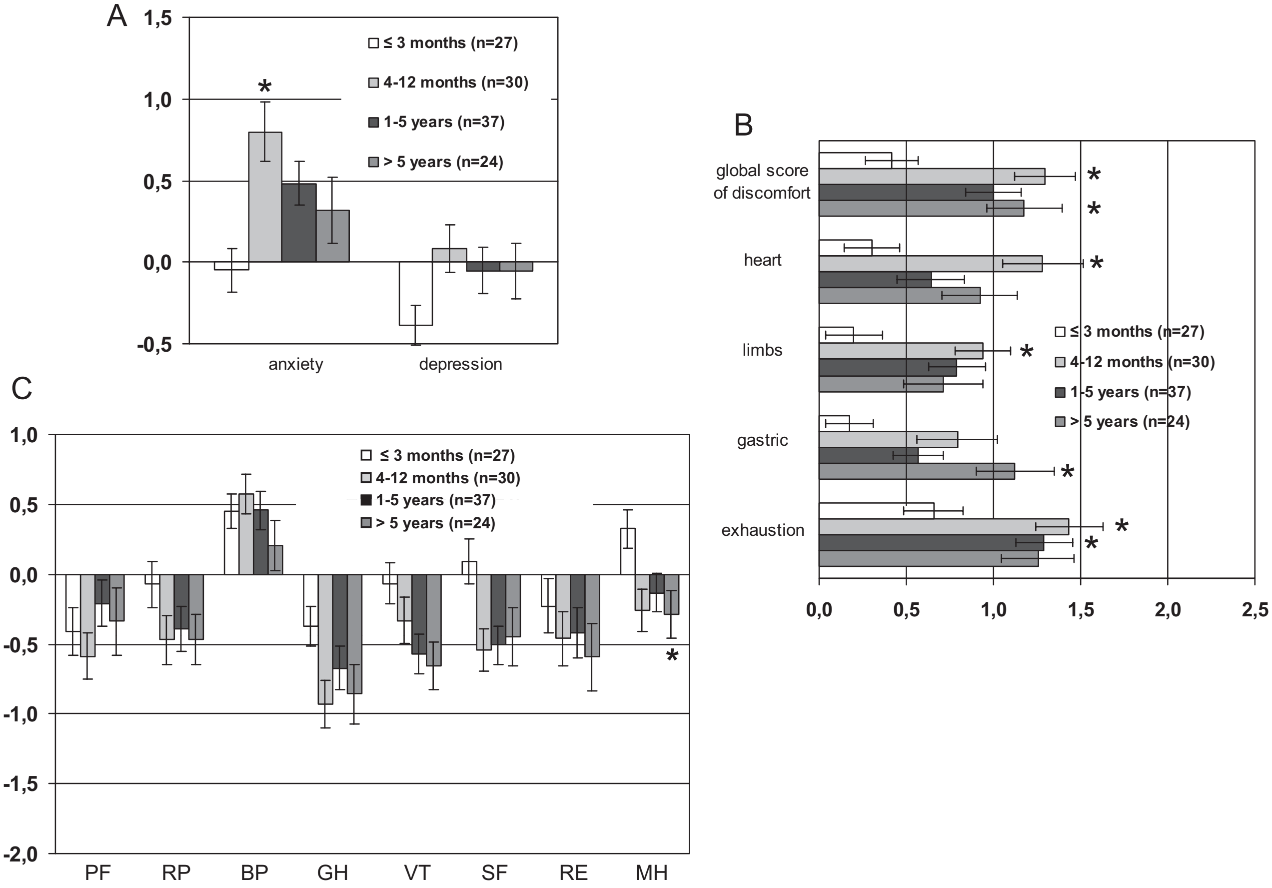

FIGURE 4. Age and sex-matched *Z* scores of the Hospital Anxiety and Depression Scale (HADS) (A), GBB-24 (B), and SF-36 (C) of patients with adrenal insufficiency (AI) depending on the time from first onset of symptoms and complaints until correct diagnosis. Subgroup analysis of nonoperated patients. Higher *Z* scores indicate higher impairment of quality of life for HADS (A) and GBB-24 (B), whereas higher scores in SF-36 (C) indicate less pain or less impaired functioning. Zero on the axis represents the normal control population. Physical functioning (PF), role functioning physical (RP), bodily pain (BP), general health perception (GH), vitality (VT), social functioning (SF), role functioning emotional (RE), and mental health (MH). $^*P < 0.05$, $^{**}P < 0.005$ compared with ≤3 months. $\#P < 0.05$ versus 1 to 5 years. $+P < 0.05$ versus 4 to 12 months.

doctors consulted. Second, because of the cross-sectional design and the specialized endocrine center and endocrine practices, there might be a selection bias. The latter may be caused also by the fact that only about half of the contacted patients agreed to participate in the study. Third, the cohort size might still be too small to detect real differences in SHS. Fourth, the questionnaires used are not specific for the evaluation of AI. The creation of AI-specific questionnaires will be a future task. However, we believe that the results of this study provide a useful and fairly accurate view of patients with AI in Germany.

TABLE 5. Occupational changes (in percent) due to their disease in patients with PAI and SAI

	Total (n = 216)	PAI (n = 99)	SAI (n = 117)
No changes	63%	72%	55%[a]
Out of work	25%	14%	33%[a]
Changed employment	4%	3%	4%
Shift work	3%	4%	2%
Reduced number of working hours	4%	5%	3%
Others	3%	2%	3%

[a] $P < 0.05$ PAI vs. SAI.
PAI, primary adrenal insufficiency; SAI, secondary adrenal insufficiency.

In conclusion, our data illustrate that patients with AI suffer from unspecific symptoms leading to a delayed diagnosis in Germany. Often several physicians have seen the patient, and frequent false diagnosis includes psychotic and psychiatric as well as gastrointestinal diseases. An early diagnosis and start of replacement therapy seem to have a positive effect on the quality of life; however, patients with AI still showed an overall significantly impaired SHS despite medical treatment. Because of the symptoms and complaints, a large number of patients were out of work and received disability pensions highlighting the socioeconomic problem in this chronic disease.

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REFERENCES

1. **Arlt W, Allolio B.** Adrenal insufficiency. Lancet 2003;361:1881–93.
2. **Arlt W.** The approach to the adult with newly diagnosed adrenal insufficiency. J Clin Endocrinol Metab 2009;94:1059–67.
3. **Oelkers W.** Adrenal insufficiency. New Engl J Med 1996;335: 1206–12.
4. **Dunlop D.** Eighty-six cases of Addison's disease. Br Med J 1963;2: 887–91.
5. **Lovas K, Loge JH, Husebye ES.** Subjective health status in Norwegian patients with Addison's disease. Clin Endocrinol (Oxf) 2002;56: 581–8.
6. **Bleicken B, Hahner S, Loeffler M, et al.** Influence of hydrocortisone dosage scheme on health-related quality of life in patients with adrenal insufficiency. Clin Endocrinol (Oxf) 2010;72:297–304.
7. **Hahner S, Loeffler M, Fassnacht M, et al.** Impaired subjective health status in 256 patients with adrenal insufficiency on standard therapy based on cross-sectional analysis. J Clin Endocrinol Metab 2007;92: 3912–22.
8. **Bleicken B, Hahner S, Loeffler M, et al.** Impaired subjective health status in chronic adrenal insufficiency: impact of different glucocorticoid replacement regimens. Eur J Endocrinol 2008;159:811–7.
9. **Ware JE Jr, Sherbourne CD.** The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473–83.
10. **Nemeth G.** Health related quality of life outcome instruments. Eur Spine J 2006;15(suppl 1):S44–51.
11. **Garratt A, Schmidt L, Mackintosh A, et al.** Quality of life measurement: bibliographic study of patient assessed health outcome measures. BMJ 2002;324:1417.
12. **Ellert U, Bellach BM.** The SF-36 in the Federal Health Survey—description of a current normal sample. Gesundheitswesen 1999;61: S184–90.
13. **Brahler E, Schumacher J, Brahler C.** First all-Germany standardization of the brief form of the Gissen Complaints Questionnaire GBB-24. Psychother Psychosom Med Psychol 2000;50:14–21.
14. **Zigmond AS, Snaith RP.** The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361–70.
15. **Hinz A, Brahler E, Schwarz R, et al.** How useful is the calculation of total scores for questionnaires concerning health related quality of life?. Psychother Psychosom Med Psychol 2005;55:221–8.
16. **Hinz A, Schwarz R.** Anxiety and depression in the general population: normal values in the Hospital Anxiety and Depression Scale. Psychother Psychosom Med Psychol 2001;51:193–200.
17. **Boccardi L, Verde M.** Gender differences in the clinical presentation to the emergency department for chest pain. Ital Heart J 2003;4:371–3.
18. **Rollman GB, Abdel-Shaheed J, Gillespie JM, et al.** Does past pain influence current pain: biological and psychosocial models of sex differences. Eur J Pain 2004;8:427–33.
19. **Helms JE, Barone CP.** Physiology and treatment of pain. Crit Care Nurse 2008;28:38–49.
20. **Rhudy JL, Williams AE.** Gender differences in pain: do emotions play a role? Gend Med 2005;2:208–26.
21. **Jeffcoate W.** Assessment of corticosteroid replacement therapy in adults with adrenal insufficiency. Ann Clin Biochem 1999;36:151–7.
22. **Johannsson G, Filipsson H, Bergthorsdottir R, et al.** Long-acting hydrocortisone for glucocorticoid replacement therapy. Horm Res 2007;68(suppl 5):182–8.
23. **Bird S.** Failure to diagnose: Addison disease. Aust Fam Physician 2007;36:859–61.
24. **Torrejon S, Webb SM, Rodriguez-Espinosa J, et al.** Long-lasting subclinical Addison's disease. Exp Clin Endocrinol Diabetes 2007;115: 530–2.
25. **Shulman DI, Palmert MR, Kemp SF.** Adrenal insufficiency: still a cause of morbidity and death in childhood. Pediatrics 2007;119:e484–94.
26. **Munver R, Volfson IA.** Adrenal insufficiency: diagnosis and management. Curr Urol Rep 2006;7:80–5.
27. **Anglin RE, Rosebush PI, Mazurek MF.** The neuropsychiatric profile of Addison's disease: revisiting a forgotten phenomenon. J Neuropsychiatry Clin Neurosci 2006;18:450–9.
28. **Bergthorsdottir R, Leonsson-Zachrisson M, Oden A, et al.** Premature mortality in patients with Addison's disease: a population-based study. J Clin Endocrinol Metab 2006;91:4849–53.
29. **Tomlinson JW, Holden N, Hills RK, et al.** Association between premature mortality and hypopituitarism. West Midlands Prospective Hypopituitary Study Group. Lancet 2001;357:425–31.