Predictors of adrenal crisis in patients with Addison's disease

Cindrić, Tea

UNIVERSITY OF ZAGREB
SCHOOL OF MEDICINE

Tea Cindrić

Predictors of adrenal crisis in patients with Addison's disease

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This research was performed in collaboration with the Department of Endocrinology at University Hospital Center Zagreb (KBC Zagreb, Rebro), under the supervision of prof. dr. sc. Tina Dušek.

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Summary

Title: Predictors of adrenal crisis in patients with Addison's disease

Author: Tea Cindrić

Addison disease is the disease of the adrenal gland in which the primary characteristic is the inability of the adrenal gland to produce cortisol and aldosterone. Patients require lifetime treatment with orally prescribed steroid drugs which replace cortisol and aldosterone. In the case of any stressful situation, from psychological stress to infection or some other acute disease, a very dangerous adrenal crisis can develop. Because of that, it is important to adapt the dose of the drugs, meaning, either increase the oral dose of hydrocortison or take it parenterally. The education of the patients about the risk factors for the crisis, symptoms of the crisis and about the way of adjustment treatment when needed is necessary. In this study, we used a questionnaire to find out how much are the patients, treated for Addison's disease in the tertiary center, informed about their disease, how many risk factors and symptoms of the crisis they know, and how much they know about dose adjustment in specific situations. Among other things, we found out that interviewed men are statistically significantly diagnosed in younger age and that they are younger at the time of research than interviewed women. Twenty-two patients were participating in our study. It is established that those patients who know more risk factors for adrenal crisis, have lower incidence of adrenal crisis (P=0.03). In conclusion, the education of patients about the risk factors which precede adrenal crisis is important in prevention of developing the crisis.

Key words: Addison's disease, hormones, stressors, adrenal crisis, risk factors, education

Sažetak

Naslov: Prediktori adrenalne krize u bolesnika s Addisonovom bolešću

Autor: Tea Cindrić

Addisonova bolest je bolest nadbubrežne žlijezde čija je primarna karakteristika nemogućnost nadbubrežne žlijezde da proizvede kortizol i aldosteron. Ta dva hormona su važna za homeostazu organizma. Najčešći simptomi bolesti su umor, gubitak na težini, hiperpigmentacija kože, niži tlak, mučnina, potreba za slanom hranom, itd. Pacijenti se najčešće liječe doma uz doživotnu hormonsku terapiju koja će zamjenjivati ta dva hormona. U slučaju raznih stresnih situacija, od psihičkih stresora do infekcije ili druge akutne bolesti, vrlo je opasan razvoj adrenalne (Addisonove) krize, stoga je vrlo važno prilagoditi terapiju, odnosno povećati oralnu dozu ili je primiti intravenski. Vrlo je bitno educirati bolesnike o rizičnim faktorima koji ga mogu dovesti u stanje krize, o simptomima kriza kako bi na vrijeme prepoznao kirzu, i o načinu prilagodbe terapije kada se nađe u takvom stanju. Pokušali smo anketom saznati koliko su dvadeset dva pacijenta upućena u svoju bolest, koliko znaju rizika i simptoma krize i koliko znaju o prilagodbi terapije u određenim situacijama. Između ostalog, saznali smo da su ispitani muškarci statistički značajnije dijagnosticirani u mlađoj dobi i da su u doba našeg istraživanja u prosjeku mlađi od ispitanih žena. Utvrdili smo da oni ljudi koji znaju više rizičnih faktora, imaju i manje kriza. Međutim, nije pronađena nikakva statistički bitna poveznica između znanja o prilagodbi terapije i simptoma s brojem kriza u životu. Zaključili smo da je vrlo važna edukacija pacijenata o rizičnim faktorima (pa tako i rizičnim ponašanjima) koji mogu dovesti do Addisonove krize jer će pacijenti onda znati što izbjegavati da se ne bi doveli u rizično stanje, i na taj će način spriječiti razvoj adrenalne krize.

Ključne riječi: Addisonova bolest, hormoni, stresori, adrenalna kriza, rizični faktori, edukacija

1. Introduction

1.1. Addison's disease

Addison's disease, also known as chronic adrenocortical insufficiency, is the disease of adrenal glands, resulting from progressive destruction of the adrenal cortex, so the glands do not produce enough of two important corticosteroid hormones, cortisol and aldosterone. It is most commonly caused by the autoimmune response of a person's immune system to adrenal glands. The immune system attacks the cortex of the adrenal glands and damages it. Other causes of the Addison's disease are: an injury to adrenal glands, infections (AIDS, tuberculosis), metastatic cancer, bleeding into the glands, surgical removal of the glands, etc (1). Due to one population-based study from The Journal of Clinical Endocrinology and Metabolism, patients with Addison's disease have a higher incidence of premature death than the healthy population compared with the healthy population. They say that the risk ratio for death was more than 2-fold higher in patients with Addison's disease. The biggest risk factors responsible for the higher mortality rate were malignant, cardiovascular, and infectious diseases (2). The disease equally occurs in both sexes. One study from European Journal of Endocrinology believe that the prognosis for Addison's disease is excellent in patients who are diagnosed later in life (3).

1.2. Cortisol and aldosterone

Cortisol is the steroid hormone produced by zona fasciculata of the adrenal gland cortex. It is released during many stressful situations controlling blood sugar levels, regulating metabolism, increasing heart rate and blood pressure (4). Also, it has an important role in reducing inflammation.

Aldosterone is the main mineralocorticoid in our body, produced by zona glomerulosa of the adrenal gland cortex. It is an important regulator for sodium conservation in kidneys, salivary glands, sweat glands and colon and an important regulator for potassium released in the urine. With these functions, it helps to maintain blood pH, blood pressure and electrolyte levels (5).

1.3. Symptoms and diagnosis

The symptoms usually develop slowly, over several months, as the hormones fade away from the body. The most common symptoms include extreme fatigue, weight loss, decreased appetite, hyperpigmentation, low blood pressure, nausea, diarrhea, vomiting, abdominal pain, irritability, depression, etc (6). Sometimes, when an acute injury, illness or stress, the symptoms can develop fast since „the stress hormone" (cortisol) is missing. The disease is diagnosed according to patient's history and physical exam, blood tests (measuring sodium, potassium, cortisol, and ACTH), ACTH stimulation test (shot of artificial ACTH is given to the patient to see the response production of corticosteroids by adrenal glands), and CT/X-ray (7).

1.4. Treatment

Life-long hormone replacement therapy is needed. Hydrocortisone, prednisone or methylprednisone is given to replace cortisol and fludrocortisone acetate to replace aldosterone. Usually, once-daily fludrocortisone and hydrocortisone (15-25 mg/d) or cortisone acetate replacement (20-35 mg/d) are given in two to three times per day in adults (8). It is also important to increase salt intake, especially during heavy exercise or hot weather (9). If the patient is ill, vomiting or under some other kind of stress, he or she should know how to adapt the dose by increasing the daily dose or administrating the parenteral hydrocortisone (10).

1.5. Adrenal crisis

Adrenal crisis or acute adrenal insufficiency is a serious event caused by a lack of corticosteroid hormones during a stressful event. If not treated, it can lead to life-threatening shock and death. Signs and symptoms include confusion, loss of consciousness or delirium, low blood pressure, hyperkalemia and hyponatremia, severe weakness, diarrhea, vomiting, pain in lower back or legs, etc. However, it is most notably accompanied by cardiovascular collapse with patients found to be in acute distress. It is a medical emergency and immediate parenteral injections of corticosteroids, dextrose and saline solution should be given. It is most commonly accompanied by cardiovascular collapse with patients found to be in acute distress. It is often hard to recognize, and treatment initiation may be delayed leading to evident morbidity and mortality in those patients (11). Some retrospective studies concluded that the risk of an adrenal crisis occurring in the patients with Addison's disease has been estimated to be 6-10 adrenal crisis per 100 patient years (12).

1.6. Patients' education and knowledge

Every patient should know how to manage Addison disease during acute illnesses or any kind of stress that is affecting the body in order to efficiently prevent life-threatening adrenal crisis. The patient needs to be informed about the medication, its daily dosages, dosages in acute illness or the way of taking the drugs during illness with vomiting (13). Vomiting of oral drugs is a problem because the drug is not taken up by the body and the patient stays without the critical hormones putting itself in the dangerous risk of adrenal crisis. In cases like that, the parenteral injections of the drug should be administered. If the patient is ill without vomiting, it is essential to know that the drug dose should be increased to mimic physiological changes in cortisol secretion during stress. A research published in European Journal of Endocrinology found that adrenal crisis occurs despite good education of patients what indicates the need for improved prevention strategies (14). Another study published in The Journal of Clinical Endocrinology & Metabolism found that 18% of the patients who had the adrenal crisis did not adapt their oral GC dose despite reinstructions at study start. Despite empirical knowledge that the

improvement in education of the patients with Addison's disease will reduce the incidence of adrenal crisis, there are studies that were examining the level of the education of the patients with Addison's disease about their knowledge related to the Addison's disease are scarce (15). In our study we examined the level of knowledge of the patients treated in a tertiary center fod Addison's disease about their own treatment and the prevention of its complications.

2. Hypothesis and aims

Patients with better knowledge about etiology and about the principles of treatment of Addison disease have a lower incidence of adrenal crisis.

The main aim of the study is to find out how well are the patients with Addison disease educated about their disease and its treatment .

Secondary aims:

- to explore the incidence of Addisonian crisis among the patients with Addison's disease treated in a tertiary center
- to explore the predictive factors for the evolvent of Addisonian crisis based on patient's characteristics

3. Materials and methods

The study was performed via a telephone survey. Telephone numbers from patients who are treated for Addison disease on the Endocrinology department at KBC Zagreb (Rebro) were collected from the BIS (Bolnički informacijski sustav- the computer program with patients' information). In the beginning, we had twenty-five telephone numbers, but three patients refused to participate, so in the end, we managed to question twenty-two patients. Each questionnaire was composed of fifteen questions including the questions about age, sex, cause of their disease, knowledge about the risks and symptoms of adrenal crisis and also about the hormones they are lacking, questions about their experience with adrenal crisis and what was the cause, information about their drugs and dosages and their education about managing the dosages and the way of administration while they are ill or vomiting, and also if they have a back up drug somewhere if they forget to take it or if they have a glucocorticoid injection kit.

Statistical analysis was done using Statistical Package for the Social Sciences (SPSS) version 17.0 for Windows. Because of small sample size variables were described as median and minimum-maximum range (and interquartile range) and nonparametric statistical tests were used. Nominal variables were presented as frequencies. The difference between two independent nominal variables was tested using the χ 2 test (Fisher's exact test). The difference between two independent numerical variables was tested using the Mann-Whitney test. Significant level was accepted at $P<0.05$.

The study is approved by the hospital Ethical committee.

4. Results

4.1. Characteristics of patients with Addison's disease

At the beginning of the study, phone numbers of twenty-five patients were collected. Of 25 patients, three refused to participate in the study, so in the end, we got answers from 22 patients. Of these, 8 are males and 14 are females, also, 18 of them are living in the city, and 4 in the country. The median age of the participants is 43.5 years, and the median age at diagnosis of Addison's disease is 36.5 years. Most of the people (14/22) have the disease for more than three years, and the most common cause is due to autoimmune origin (19/22). Some people (5/22) knew the origin of their disease, but most of them (17/22) did not know so we found that information in their medical charts. An equal number of people (11/22) have experienced the adrenal crisis in life as those who have not. Four out of 22 did not know the names of adrenal hormones which are missing in the Addison's disease. From their answers on questions about awareness of symptoms and risk factors for the crisis, 12 people know more than three risk factors and 13 out of 22 know more than three symptoms of adrenal crisis. Majority (18/22) have a back-up drug somewhere if they forgot to take it at home. All these characteristics of patients with Addison's disease are seen in Table 1.

Table 1. Characteristics of patients with Addison's disease (N = 22)

Characteristic	Value
Gender (n)	
Males	8
Females	14
Age at research (years)	median 43.5 (min. 25 – max. 75) IQR* 32.5 – 54.3
Age at diagnosis of Addison's disease (years)	median 36.5 (min. 8 – max. 66) IQR* 25.5 – 45.5
Duration of Addison's disease (n)	
≤ 3 years	8
>3 years	14
Cause of Addison's disease (n)	
Autoimmune	19
Unknown	3
Place of residence (n)	
City	18
Country	4

Knowledge about the cause of Addison's disease (n)	
Yes	5
No	17
Experience of adrenal crisis (n)	
Yes	11
No	11
Number of adrenal crisis in life	median 0.5 (min. 0 – max. 15) IQR* 0 - 1
Number of known risk factors for adrenal crisis (n)	
≤ 3	10
>3	12
Number of symptoms of adrenal crisis (n)	
≤ 3	9
>3	13
Knowledge about lacking hormones (n)	
Yes	8
No	14
Having a back-up drug at home (n)	
Yes	18
No	4

*interquartile range

4.2. The difference in characteristics of patients with Addison's disease in respect to the history of adrenal crisis

We divided patients into two groups (Table 2) based on the history of adrenal crisis. First comprised patients who experienced an adrenal crisis during their life (N=11), and in the second are those who have never experienced adrenal crisis (N=11). We noticed that patients who had experienced adrenal crisis knew significantly less risk factors for the development of crisis than those patients who have never had adrenal crisis in their lives (P=0.03).

Table 2. The difference in characteristics of patients with Addison's disease in respect to the history of adrenal crisis (N = 22)

	History of adrenal crisis		
Characteristic	**Yes (n=11)**	**No (n=11)**	**P**
Gender (n) **Males** **Females**	 4 7	 4 7	>0.999*
Age at research (years)	median 43 (min. 28 –max. 72) IQR† 34 - 57	median 46 (min. 25 – max. 67) IQR† 28 - 52	0.606†
Age at diagnosis of Addison's disease (years)	median 36 (min. 8 – max. 66) IQR† 24 - 55	median 37 (min. 20 – max. 66) IQR† 27 - 43	0.949†
Duration of Addison's disease (n) **≤ 3 years** **>3 years**	 3 8	 5 6	0.659*
Cause of Addison's disease (n) **Autoimmune** **Unknown**	 10 1	 9 2	> 0.999*
Place of residence (n) **City** **Country**	 9 2	 9 2	> 0.999*
Knowledge about the cause of Addison's disease (n) **Yes** **No**	 1 10	 4 7	0.311*
Number of known risk factors for adrenal crisis (n) **≤ 3** **>3**	 8 3	 2 9	**0.03***
Number of known symptoms of adrenal crisis (n) **≤ 3** **>3**	 6 5	 3 8	0.387*

Knowledge about lacking hormones (n)			
Yes	5	3	0.659*
No	6	8	
Having a back-up drug			
Yes	9	9	> 0.999*
No	2	2	

*Fisher's exact test; †interquartile range; Mann-Whitney U test

4.3. The difference in characteristics of patients with Addison's disease in respect to the gender

When patients were divided by gender, it was found that male patients were younger than female (P=0.024), and diagnosed at younger age that women with median of 27 years (P=0.026).

Table 3. The difference in characteristics of patients with Addison's disease in respect to the gender (N = 22)

Characteristic	Males (n=8)	Female (n=14)	P
History of adrenal crisis (n)			
Yes	4	7	>0.999 *
No	4	7	
Age at research (years)	median 36 (min. 25 –max. 55) IQR† 30- 42	median 48 (min. 26 – max. 72) IQR† 39 - 57	**0.024**†
Age at diagnosis of Addison's disease (years)	median 27 (min. 20 – max. 37) IQR† 22 - 32	median 41 (min. 8 – max. 66) IQR† 27 - 55	**0.026**†
Duration of Addison's disease (n)			
≤ 3 years	3	5	0.933*
>3 years	5	9	
Cause of Addison's disease (n)			
Autoimmune	8	11	0.159*
Unknown	0	3	

Place of residence (n) **City** **Country**	 7 1	 11 3	0.603*
Knowledge about the cause of Addison's disease (n) **Yes** **No**	3 3	2 12	0.211*
Number of known risk factors for adrenal crisis (n) **≤ 3** **>3**	4 4	6 8	0.746*
Number of known symptoms of adrenal crisis (n) **≤ 3** **>3**	4 4	5 9	0.512*
Knowledge about lacking hormones (n) **Yes** **No**	4 4	4 10	0.315*
Having a back-up drug **Yes** **No**	 6 2	 12 2	0.531*

*Fisher's exact test; †interquartile range; Mann-Whitney U test

In Figure 1. the population of people with Addison's disease is divided by gender. Although males experienced more adrenal crisis and on average knew less risk factors for the development of the crisis, the difference was not proven to be statistically significant.

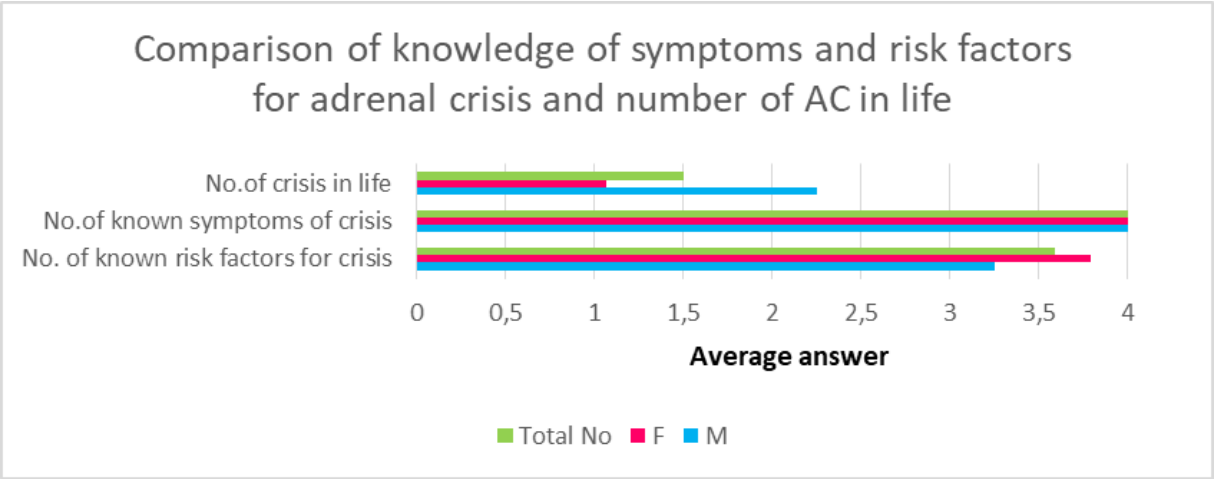

Figure 1. Comparison of knowledge of symptoms and risk factors for adrenal crisis and number of adrenal crises in life (AC=adrenal crisis)

In Figure 2., we compared the knowledge of patients who had and who haven't experienced adrenal crisis about the treatment of adrenal crisis. The studied parameters were: knowledge about adapting the dosage of the drug in certain illnesses (with and without vomiting), having a back-up drug and glucocorticoid injection kit. No statistically significant difference was found between patients with and without adrenal crisis with respect to the above mentioned characteristics.

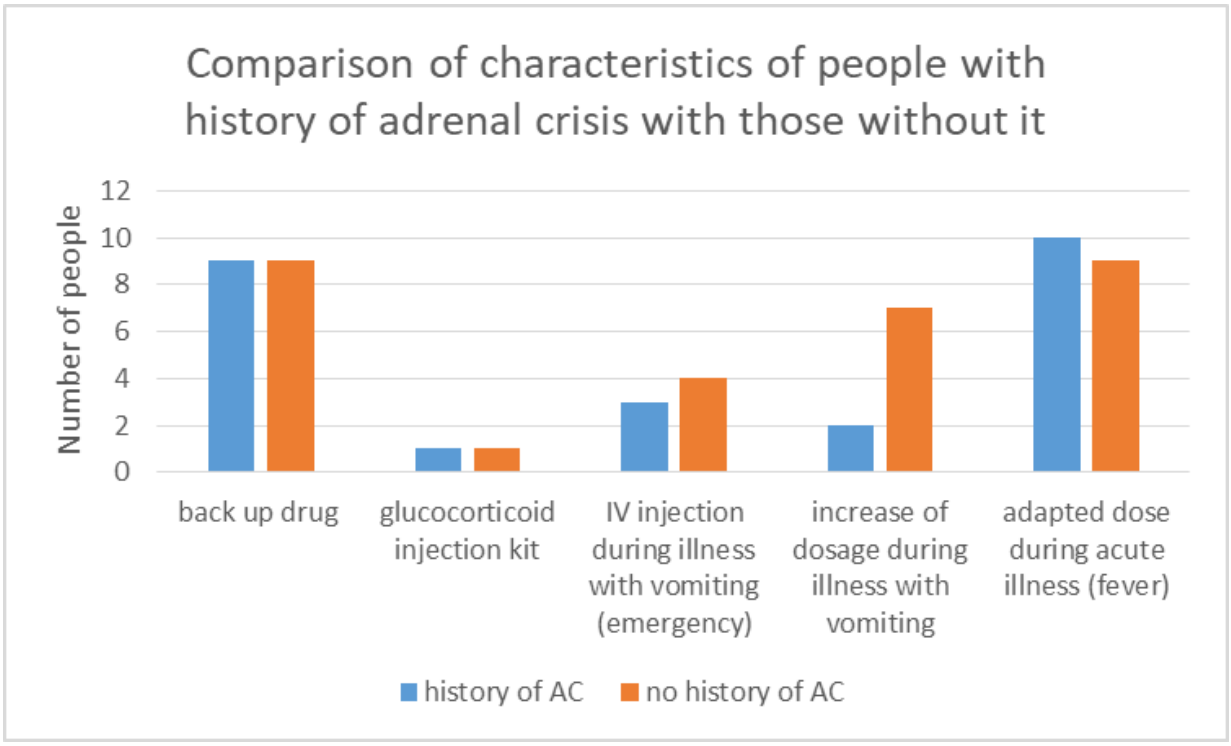

Figure 2. Comparison of characteristics of people with the history of adrenal crisis with those without it (AC=adrenal crisis)

The most common causes of the adrenal crisis are presented in Figure 3. Causes included: emotional stress, infection, vomiting, dehydration and not taking the drugs on time.

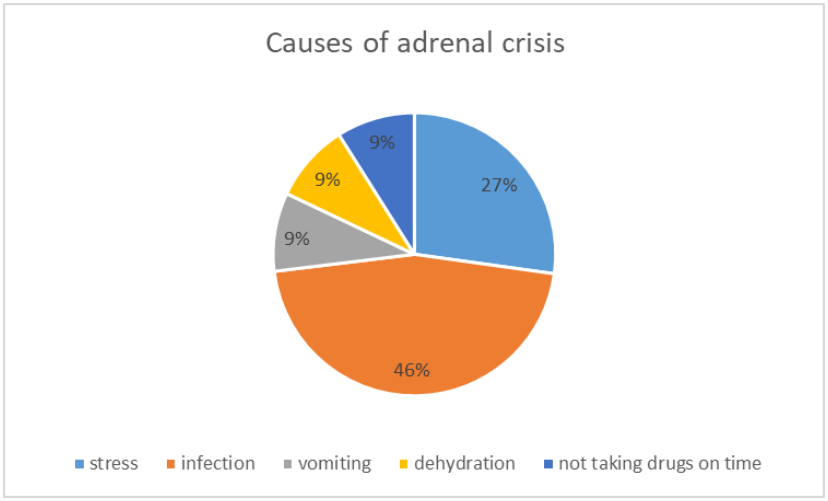

Figure 3. Causes of adrenal crisis as reported by the patients

5. Discussion

Our study examined the general knowledge of patients with Addisons disease about the treatment of their disease and prevention of its complications. According to our results, majority of patients are well educated about the symptoms of adrenal crisis and risk factors for its development. Majority of them possess back-up drug at home for the case of shortage. At the same time, minority of patients knows the names of the hormones which are missing in Addison disease, which is less important, but still reflects that they miss the theoretical knowledge about their disease.

Half of the patients in our study group experienced adrenal crisis during their life which is quite high incidence. According to our results it seems that the improvement of the knowledge of risk factors for the development of crisis might lower the crisis incidence because patients with better knowledge of risk factors had lower incidence of adrenal crisis. A recently published prospective multicenter study examining the incidence of adrenal crisis found its incidence to be 8.3 per 100 patient-years (15). They also found that adrenal crises are occuring despite patient's excellent knowledge about its treatment and prevention.

It is evident from Table 2 that people with the longer duration of the disease had a higher number of adrenal crises in life, although that data didn't reach statistical significance. It is obvious that people with longer duration of the disease have had more adrenal crises than those who are recently diagnosed simply because they had more chances and probably experienced more situations which present risk factors for developing the crisis.

There are not many differences regarding the general knowledge about the disease and treatment between genders. Concerning gender differences, we noticed statistical difference regarding age of diagnosis and it seems that in our study group men are diagnosed at younger age. Our data showed that their median age at diagnosis is 27 in men, which is even 14 earlier than in women (their median age at diagnosis is forty-one).

Our study is one of the rare studies that examined the knowledge of the patients with Addisons disease about the disease treatment. Probable reason for that lays in the fact that Addison disease is quite rare disease. Small number of study participants therefore represents the major limitation of our study. Another limitation is that study is of the retrospective character and the data collected are based on the patient's recall about their experience of adrenal crisis. Certainly, further studies are needed to explore to which extent is the patient's knowledge about Addison disease treatment crucial in the prevention of the life threatening condition such as adrenal crisis. According to our results, it seems that the improvement in the knowledge about the potential risk factors for the development of adrenal crisis might lower its incidence.

6. Conclusion

Patients who know more risk factors for the development of adrenal crisis, have experienced fewer adrenal crises in their life. It is important to educate patients about the risk factors for adrenal crisis so they can be more cautious and experience less episodes of this life-threatening condition.

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9. Biography

Datum rođenja: 14/09/1994
Državljanstvo: hrvatsko
Spol: Žensko

Obrazovanje:
2014 - 2021 Medicinski fakultet, Sveučilište u Zagrebu
2009 - 2013 VII. Gimnazija
2001 – 2009 Osnovna škola Vladimira Nazora

Iskustvo:
2019. Božićno darivanje djece u bolnicama (Studentska sekcija za pedijatriju)
2017. – 2018. demonstrator za histologiju, Medicinski fakultet (Zavod za histologiju i embriologiju)
2018 dodjela nagrade Vesna Andrijević Matovac (nagrada VAM), Udruga SVE za NJU
2018 International program, Croatian Medical Students' International Committee (CroMSIC)
2018 dijeljenje letaka i ljepljenje plakata, Croatian Medical Student's International Committe (CroMSIC)
2015 – 2016 demonstrator za fiziku, Medicinski fakultet (Zavod za fiziku)
2015 Bolnica za medvjedića, European Medical Student's Association Zagreb

Jezične vještine:
Materinski jezik/jezici: hrvatski
Drugi jezici:
engleski C1
francuski A2
njemački A2

NAGRADE:
Dekanova nagrada za najbolji znanstveni rad studenata u akademskoj godini 2018./2019. – Medicinski fakultet, Zagreb
Predictor of adrenal crisis in patients with Addison's disease

ČLANSTVA:
2015 – 2021
Croatian Medical Stuedents' International Committe (CroMSIC)
Zagreb