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Cushing's disease – cardiovascular and metabolic complications

Choroba Cushinga – powikłania sercowo-naczyniowe oraz metaboliczne

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Abstract

Cushing's disease is excess cortisol level due to increased adrenocorticotropin secretion from pituitary adenoma. Incidence rate is 2–3 cases per year and the prevalence is 40 per 1 million people. It affects mostly young adults with high prevalence in women (incidence rate is 3–8 fold higher than in men). Cushing's disease can generate metabolic and cardiovascular complications. **Aim:** The aim of this paper was to estimate the incidence of cardiometabolic complications, such as hypertension, diabetes, prediabetes, overweight and obesity and their relationships with age, sex and body mass index. **Material and methods:** A total of 79 presurgical patients with Cushing's disease were enrolled. All patients were examined and their medical documentation was thoroughly analysed with special regard to demographic data, the underlying disease and concomitant diseases (especially diabetes, prediabetes, hypertension, overweight and obesity). **Results:** Mean body mass index (BMI) was 31.07 ± 6.97 kg/m². Obesity (BMI ≥ 30 kg/m²), overweight (BMI 25–30 kg/m²) and normal body weight were reported in 37 (46.8%), 29 (36.7%) and 13 (16.5%) patients, respectively. Diabetes and prediabetes were diagnosed in 27 (34.2%) and 29 (36.7%) patients, respectively. The remaining 23 (29.1%) patients had normal glucose levels. Hypertension was confirmed in 64 of 79 (81%) patients; 15 (19%) patients had normal blood pressure. **Conclusions:** Complications like high BMI, impaired glucose metabolism and hypertension were diagnosed in the majority of patients: 66 (83.5%), 56 (70.9%) and 64 (81%), respectively. The risk of these complications increased with age.

Keywords: Cushing's disease, hypercortisolism, complications

Streszczenie

Wprowadzenie: Choroba Cushinga jest stanem hiperkortyzolemii wynikającym z nadprodukcji hormonu adrenokortykotropowego przez gruczolak przysadki. Zachorowalność na tę chorobę wynosi 2–3 przypadki na 1 mln mieszkańców/rok, natomiast chorobowość – 40 osób/1 mln osób. Kobiety chorują istotnie częściej; szacuje się, że zapadalność wśród kobiet jest 3–8-krotnie większa w porównaniu z mężczyznami. Choroba Cushinga może się wiązać z wystąpieniem powikłań o charakterze metabolicznym oraz sercowo-naczyniowym. **Cel pracy:** Cele pracy obejmowały ocenę częstości występowania powikłań choroby Cushinga, ze szczególnym uwzględnieniem powikłań sercowo-naczyniowych pod postacią nadciśnienia tętniczego oraz metabolicznych o charakterze zaburzeń gospodarki węglowodanowej i nieprawidłowej masy ciała, jak również analizę zależności między wiekiem, płcią i masą ciała chorych a poszczególnymi powikłaniami hiperkortyzolemii. **Materiał i metody:** Do badania włączono 79 kolejnych pacjentów z chorobą Cushinga. Wszyscy chorzy zostali poddani pełnemu badaniu podmiotowemu oraz przedmiotowemu. Ponadto dokonano analizy dotychczasowej dokumentacji medycznej, ze szczególnym uwzględnieniem danych demograficznych, informacji dotyczących rozpoznania choroby podstawowej oraz chorób współistniejących (cukrzyca, stanu przedcukrzycowego, nadciśnienia tętniczego, nadwagi oraz otyłości). **Wyniki:** Średni wskaźnik masy ciała (*body mass index*, BMI) wynosił $31,07 \pm 6,97$ kg/m². Otyłość (BMI ≥ 30 kg/m²), nadwagę (BMI 25–30 kg/m²) i prawidłową masę ciała stwierdzono odpowiednio u 37 (46,8%), 29 (36,7%) i 13 (16,5%) pacjentów. U 27 (34,2%) pacjentów stwierdzono cukrzycę, u 29 (36,7%) osób stan przedcukrzycowy, a u pozostałych 23 (29,1%) prawidłową tolerancję węglowodanów. Nadciśnienie tętnicze potwierdzono u 64 z 79 (81%) pacjentów, a u pozostałych 15 (19%) odnotowano prawidłowe wartości ciśnienia tętniczego. **Wnioski:** W badanej grupie powikłania pod postacią nieprawidłowego BMI, zaburzeń gospodarki węglowodanowej oraz nadciśnienia tętniczego występowały u większości chorych, stanowiąc odpowiednio 66 (83,5%), 56 (70,9%) oraz 64 (81%) badanych. Prawdopodobieństwo wystąpienia wszystkich analizowanych schorzeń nasilało się wraz z wiekiem pacjentów.

Słowa kluczowe: choroba Cushinga, hiperkortyzolemia, powikłania

INTRODUCTION

Cushing's disease is excess cortisol level due to increased adrenocorticotropin (ACTH) secretion from pituitary adenoma. Incidence rate is 2–3 cases per 1 million people per year and the prevalence is 40 per 1 million people. Women are significantly more frequently affected; it is estimated that the disease is 3–8 times more common in females vs. males. Hypercortisolism may cause metabolic and cardiovascular complications as well as severe infections. The mortality in untreated or ineffectively treated patients mostly results from these complications and is 4 times that of the general population. The 5-year survival rate is estimated at 50%^(1,2). Therefore, effective and rapid diagnosis of both the underlying disease and the overlapping diseases is a key element of care in this group of patients.

AIM

The aim of this paper was to estimate the incidence of cardiometabolic complications of Cushing's disease, with particular emphasis on hypertension, carbohydrate metabolism disorders, overweight and obesity. We also assessed the relationships between these complications and demographic and clinical parameters.

MATERIAL AND METHODS

A total of 79 subsequent patients with confirmed Cushing's disease diagnosed between 2013 and 2016 and qualified for surgical treatment were enrolled into the study. All patients were informed about the aims and the method of the study and gave their consent to participate in the study. The study was approved by the Bioethics Committee of the Military Institute of Medicine (No. 40/WIM). Medical history was collected and a full clinical examination was performed in all patients. Furthermore, we analysed medical records with particular regard to demographic data, the underlying disease and comorbidities (diabetes, prediabetes, arterial hypertension, overweight and obesity).

Overweight was defined as body mass index (BMI) ≥ 25 kg/m², obesity was defined as BMI ≥ 30 kg/m². BMI was assessed using a standard formula: body weight [kg]/height [m]².

Prediabetes and diabetes were diagnosed in accordance with the guidelines of the Polish Diabetes Association or based on an earlier diagnosis reported in patient's records⁽³⁾. Arterial hypertension was diagnosed if the patient was already on hypotensive therapy or when average resting blood pressure was higher than 140/90 mm Hg in 3 consecutive measurements taken within 15 minutes.

RESULTS

The study group included 79 patients with Cushing's disease, 66 (83.5%) women and 13 (16.5%) men. Female/male

| Characteristics | | | Value |
|--------------------------|----------|--------------|-----------|
| Total number of patients | | | 79 |
| Age (years) | Mean | | 43.75 |
| | $\pm SD$ | | 14.88 |
| | Median | | 42.7 |
| | Range | | 17–79 |
| Sex | Women | <i>n</i> (%) | 66 (83.5) |
| | Men | <i>n</i> (%) | 13 (16.5) |
| BMI (kg/m ²) | Mean | | 31.07 |
| | $\pm SD$ | | 6.97 |
| | Median | | 29.74 |
| | Range | | 16.8–49.6 |

Tab. 1. Study group characteristics – basic data

ratio was 5:1. Patients' mean age was 43.75 ± 14.88 years (median: 42.7; range: 17–79 years). Mean female age was 43.8 ± 15.1 years (median: 43.2; range: 16.7–78.8 years). Mean male age was 43.4 ± 14.1 years (median: 43.8; range: 24.7–70.7 years). The *t*-test showed no statistically significant age differences between women and men ($p = 0.926$) (Tab. 1).

We analysed the incidence of hypercortisolism complications, considering patients' age and sex. Data on the incidence of complications are shown in Tab. 2.

Mean BMI was 31.07 ± 6.97 kg/m² (median: 29.74 kg/m²; range: 16.8–49.6 kg/m²). Obesity (BMI ≥ 30 kg/m²), overweight (BMI 25–30 kg/m²) and normal body weight were reported in 37 (46.8%), 29 (36.7%) and 13 (16.5%) patients, respectively. The *t*-test showed no statistically significant differences in BMI between women and men – 30.83 ± 6.95 kg/m² (median: 29.68 kg/m²; range: 16.8–49.6 kg/m²) vs. 32.32 ± 7.18 kg/m² (median: 30.86 kg/m²; range: 24.8–47 kg/m²) ($p = 0.485$). A total of 30 (45.5%) women and 7 (53.8%) men were classified as obese. Overweight was reported in 24 (36.4%) women and 5 (38.5%) men, whereas normal BMI was reported for 12 (18.2%) women and 1 (7.7%) man. The Fisher's exact test did not confirm the difference between BMI categories (obesity, overweight and normal body weight) and sex ($p = 0.785$).

Mean age was 44.94 ± 15.38 years (median: 44.1 years) in patients with obesity, 46.55 ± 13.5 years (median: 51.4 years) in overweight patients, and 34.08 ± 13.37 years (median: 28.3 years) in patients with normal body weight. The analysis of variance showed that these differences were

| Hypercortisolism complications | | Results – <i>n</i> (%) |
|----------------------------------|-------------|------------------------|
| Abnormal BMI | Obesity | 37 (46.8) |
| | Overweight | 29 (36.7) |
| Impaired carbohydrate metabolism | Diabetes | 27 (34.2) |
| | Prediabetes | 29 (36.7) |
| Hypertension | | 64 (81) |

Tab. 2. Study group characteristics – hypercortisolism complications

| Hypercortisolism complications | | Age (years \pm SD) | p |
|----------------------------------|-------------|-------------------------|-----------------------|
| Abnormal BMI | Obesity | 44.94 \pm 15.38 | p = 0.032* |
| | Overweight | 46.55 \pm 13.52 | |
| Normal BMI | | 34.08 \pm 13.38 | |
| Impaired carbohydrate metabolism | Diabetes | 52.66 \pm 14.17 | p < 0.001* |
| | Prediabetes | 39.36 \pm 14.68 | |
| Normal glucose levels | | 38.81 \pm 11.37 | |
| Hypertension | | 46.76 \pm 14.6 | p < 0.001** |
| Normal blood pressure | | 30.87 \pm 7.47 | |

* Analysis of variance. ** t-test.

Tab. 3. Study group characteristics – correlations between hypercortisolism and age

| Hypercortisolism complications | | BMI (kg/m ² \pm SD) | p |
|----------------------------------|--------------|-------------------------------------|--------------------|
| Impaired carbohydrate metabolism | Diabetes | 32.82 \pm 7.76 | p = 0.078* |
| | Pre-diabetes | 30.82 \pm 6.05 | |
| Normal glucose levels | | 29.34 \pm 6.89 | |
| Hypertension | | 32.03 \pm 6.78 | p = 0.011** |
| Normal blood pressure | | 26.98 \pm 6.43 | |

* For a linear trend. ** t-test.

Tab. 4. Study group characteristics – correlations between hypercortisolism and BMI

statistically significant ($p = 0.032$). We therefore confirmed that obesity and overweight were more common among older patients with Cushing's disease.

Diabetes was found in 27 (34.2%), prediabetes in 29 (36.7%), and normal carbohydrate tolerance in 23 (29.1%) patients. The Fisher's exact test showed no significant differences in carbohydrate metabolism between women and men ($p = 0.220$). Diabetes was found in 25 (37.9%) women and 2 (15.4%) men, prediabetes was reported in 24 (36.4%) women and 5 (38.5%) men, while normal carbohydrate metabolism was reported for 17 (25.8%) women and 6 (46.2%) men. The mean age of patients with diabetes was 52.66 \pm 14.17 years (median: 54.4 years), the mean age of patients with prediabetes was 39.36 \pm 14.58 years (median: 39.3 years), and the mean age of patients with normal carbohydrate metabolism was 38.81 \pm 11.37 years (median: 36.4 year). The analysis of variance confirmed that these differences were statistically significant ($p < 0.001$). It was therefore confirmed that the risk of carbohydrate metabolism disorders increases with age in patients with Cushing's disease. The mean BMI was 32.82 \pm 7.76 kg/m² (median: 29.61 kg/m²) in the group of diabetic patients, 30.82 \pm 6.05 kg/m² (median: 30.12 kg/m²) in prediabetic patients, and 29.34 \pm 6.89 kg/m² (median: 29.8 kg/m²) in patients with no carbohydrate metabolism disorders. It was therefore shown (on the border of significance) that there was an association between increased BMI and carbohydrate metabolism disorders in Cushing's disease ($p = 0.078$).

Arterial hypertension was confirmed in 64 out of 79 (81%) patients, while normal blood pressure was reported for the other 15 (19%) patients. Hypertension was found in 53 (80.3%) women and 11 (84.6%) men. Normal blood pressure was reported for 13 (19.7%) women and 2 (15.4%) men. The Fisher's exact test showed no statistically significant differences in the incidence of arterial hypertension between men and women ($p = 1.000$). The mean age was 46.76 \pm 14.6 years (median: 48.5 years) for patients with arterial hypertension, and 30.87 \pm 7.47 years (median: 32.2 years) for patients with normal blood pressure. *t*-test showed that the differences were statistically significant ($p < 0.001$). The mean BMI was 32.03 \pm 6.78 kg/m² (median: 30.3 kg/m²) in patients with hypertension, and 26.98 \pm 6.42 kg/m² (median: 26.4 kg/m²) in patients with normal blood pressure. *t*-test showed that the differences were statistically significant ($p = 0.011$). It was therefore shown that arterial hypertension was associated with advancing age and higher BMI in patients with Cushing's disease. The relationships between hypercortisolism complications and age are shown in Tab. 3. The associations between complications and BMI are presented in Tab. 4.

DISCUSSION

The study assessed complications in the form of abnormal body weight (overweight and obesity), carbohydrate metabolism disorders (prediabetes and diabetes), and arterial hypertension. We are convinced that these are the key elements in the assessment of the risk of mortality, and, at the same time, they may be diagnosed and characterised based on uniform criteria and recommendations of academic societies. Obesity and overweight are the most common complications in Cushing's disease^(1,4-6). The mean BMI in the study group was 31.07 \pm 6.97 kg/m², indicating mean body weight corresponding to first-degree obesity, as in accordance with the World Health Organization criteria⁽⁷⁾. Patients with obesity and overweight accounted for 46.8% and 36.7%, respectively, which totals to more than 80% of the study group. No statistically significant differences in BMI were found between men and women ($p = 0.485$). These data correspond with the data presented by Pecori Giraldi et al. in their study in 280 patients with Cushing's disease, who showed abnormal body weight in up to 85.1% of patients⁽⁸⁾ as well as with the findings of other authors^(1,4,5). It can be therefore concluded that the group in question is representative of patients with Cushing's disease in terms of metabolism and anthropometry. Furthermore, it should be noted that the incidence of obesity and overweight increased with patient's age, and that patients with normal BMI were on average 10 years younger than those with Cushing's disease and obesity, which confirms the fact that hypercortisolism does not induce obesity in patients, but only increases tendencies that are also found in hypercortisolism-free population. Also, the analysis of

the BMI distribution showed that, contrary to common beliefs, patients with hypercortisolism do not present with morbid obesity, but rather overweight and class I obesity. This fact may be associated with the catabolic effects of hypercortisolism on bone mass, muscles, and adipose tissue redistribution, rather than its general increase. However, detailed analysis of these associations goes beyond the framework of this study.

Obesity and overweight are often associated with impaired carbohydrate metabolism. In our group of patients, diabetes and prediabetes were reported for 71% of patients. Diabetic and prediabetic patients accounted for 34.2% and 36.7%, respectively. No statistically significant differences were found in the incidence of carbohydrate metabolism disorders between men and women. Incidence rates ranging between 13% and 47% for diabetes and between 40% and 70% for impaired carbohydrate metabolism are reported in the literature^(9,10). The relatively large differences in the incidence of diabetes in patients with Cushing's disease are most likely due to the underestimation of the phenomenon in some of the studies, or improper qualification of carbohydrate metabolism due to a failure to perform oral glucose tolerance test at normal or slightly increased fasting glucose levels. In our study, the diagnostic criteria for carbohydrate metabolism disorders were in line with the recommendations of the Polish Diabetes Association, unchanged since 2012⁽³⁾.

It is noteworthy that, as in the case of abnormal BMI, the risk of diabetes also increases with age so that patients with Cushing's disease and diabetes are almost 15 years older than those with normal carbohydrate metabolism (mean: 52.8 vs. 38.8 years). This indicates that more advanced age of patients with Cushing's disease predisposes to carbohydrate metabolism disorders. This possibility was also suggested by other authors^(11,12). Furthermore, similarly to the general population, there is a relationship (on the border of statistical significance) between increased body weight and the incidence of impaired carbohydrate metabolism in the study group. This is an argument for including education on diet, moderate physical exercise and healthy lifestyle in the causative treatment of Cushing's disease to additionally modify the risk of metabolic complications of this devastating condition.

Arterial hypertension is another easily detectable and measurable complication of Cushing's disease. It was found in 64 out of 79 patients, accounting for 81% of study participants. This incidence corresponds to that reported by other authors^(1,4,6,12). No sex differences were observed in the incidence of hypertension (men: 80.3%, women: 84.6%). However, the relationship between arterial hypertension and age and excess body weight, which is also typical of the general population, was confirmed. A mean age of 46.76 ± 14.6 years was reported for patients in the group with confirmed hypertension and 30.87 ± 7.47 years – in the group of patients with normal blood pressure ($p < 0.001$). A similar association was

observed for arterial hypertension and increased BMI. Similar findings were presented by the authors of the Ancona Consensus⁽¹⁾. Arterial hypertension, which increases the cardiovascular risk in the general population, is significantly more common in patients with Cushing's disease compared to individuals with no hypercortisolism; therefore, monitoring and optimised control of blood pressure seem necessary in these patients. This is the best and safe way to prepare them for surgical treatment as well as to reduce the cardiovascular risk, which persists for up to 5 years after successful surgical treatment of Cushing's disease, as pointed out by Faggiano et al. and Colao et al.^(4,13,14).

CONCLUSIONS

A high incidence of cardiometabolic complications, such as obesity, overweight, carbohydrate metabolism disorders and hypertension, is seen in Cushing's disease. These complications were observed in the majority of patients in the study group, i.e. in 37 (46.8%), 29 (36.7%), 56 (70.9%) and 64 (81%) patients, respectively. The incidence of these complications increased with age. A relationship was shown between increased BMI and the incidence of hypertension and carbohydrate metabolism disorders in Cushing's disease. No association was found between the above complications and sex.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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