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SADRŽAJ

NAGRAĐENI U KATEGORIJI NAJBOLJEG MLADOG ZNANSTVENIKA

S1 Kako zaustaviti ciklus pretjeranog upalnog odgovora u bolesnika sa šećernom bolesti tipa 2?

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Uvod s ciljem: Kronična upala niskog stupnja ima ključnu ulogu u razvoju i progresiji šećerne bolesti tipa 2 te njezinih komplikacija. Iako su mehanizmi metaboličke upale djelomično istraženi, utjecaj šećerne bolesti na imunološki sustav nije u potpunosti razjašnjen. Cilj istraživanja bio je ispitati povezanost šećerne bolesti tipa 2 s proupalnim profilom antivirusnog imunološkog sustava te utvrditi može li antihiperglikemijsko liječenje utjecati na te promjene.

Metode: Iz periferne krvi osoba sa šećernom bolesti tipa 2 i kontrolne skupine izolirane su mononuklearne stanice. U podskupini bolesnika, koji su postigli ciljne vrijednosti glikiranog hemoglobina (HbA1c<7,0%), prikupljeni su uzorci krvi prije i šest mjeseci nakon optimizacije antihiperglikemijske terapije, koja je uključivala dodatak inhibitora natrij-glukoza kotransportera-2, sa ili bez agonista receptora za glukagonu sličan peptid-1, uz metformin. Fenotip, proliferacija i proizvodnja citokina citotoksičnih limfocita analizirani su protočnom citometrijom.

Rezultati: U bolesnika sa šećernom bolesti tipa 2 zabilježena je značajno veća proizvodnja čimbenika tumorske nekroze-α iz CD8+ limfocita T te granzima B iz prirodnih stanica ubojica i γδ limfocita T. Ovi su parametri pokazali pozitivnu korelaciju s dobi i trajanjem bolesti. Optimizacija antihiperglikemijske terapije rezultirala je smanjenjem proizvodnje citokina iz svih analiziranih citotoksičnih limfocita, ukazujući na potencijalnu reverzibilnost upalnih promjena povezanih sa šećernom bolesti.

Zaključak: Citotoksične imunološke stanice prolaze funkcionalne promjene u kontekstu šećerne bolesti tipa 2, što može doprinijeti razvoju i progresiji dijabetičkih komplikacija izazvanih upalom. Naša otkrića naglašavaju potencijal optimalne antihiperglikemijske terapije u moduliranju ovih imunoloških promjena, otvarajući nove mogućnosti za terapijske pristupe usmjerene na kontrolu upale kod osoba sa šećernom bolesti.

Ključne riječi: Citokini; Inhibitori prijenosnika natrija i glukoze 2; Receptor glukagonu sličnog peptida 1; Šećerna bolest, tip 2; Upala.

S1 How to break the cycle of hyperinflammatory response in patients with type 2 diabetes?

Introduction and Aim: Low-grade chronic inflammation plays a pivotal role in the development and progression of type 2 diabetes mellitus and its complications. Although the mechanisms underlying metabolic inflammation are partially understood, the impact of diabetes on the immune system remains unclear. This study aims to investigate the association between type 2 diabetes and the pro-inflammatory profile within the antiviral immune system and to determine whether antihyperglycemic therapy can mitigate these changes.

Methods: Peripheral blood mononuclear cells were isolated from patients with type 2 diabetes and the control group. In a subset of patients achieving target glycated hemoglobin (HbA1c<7.0%), blood samples were collected before and six months after optimization of antihyperglycemic therapy, including the addition of sodium-glucose cotransporter-2 inhibitors, with or without glucagon-like peptide-1 receptor agonists, alongside metformin. The phenotype, proliferation, and cytokine production of cytotoxic lymphocytes were analyzed using flow cytometry.

Results: Patients with type 2 diabetes exhibited significantly increased tumor necrosis factor-α production by CD8+ T lymphocytes and granzyme B secretion by natural killer cells and γδ T lymphocytes. These parameters showed a positive correlation with age and disease duration. Optimization of antihyperglycemic therapy led to a reduction in cytokine production across all analyzed cytotoxic lymphocytes, suggesting a potential reversibility of diabetes-associated inflammatory changes.
Conclusion: Cytotoxic immune cells undergo functional alterations in type 2 diabetes, potentially contributing to inflammation-driven diabetic complications. Our findings highlight the potential of optimal antihyperglycemic therapy in modulating these changes, opening new avenues for novel therapeutic strategies targeting inflammation in diabetes management.

Keywords: Cytokines; Glucagon-like peptide-1 receptor agonists; Inflammation; Sodium-glucose cotransporter-2 inhibitors; Type 2 diabetes mellitus.

S2 Učinak povećanja inzulinske osjetljivosti na metaboličke i reproduktivne ishode u žena sa sindromom policističnih jajnika i prekomjernom tjelesnom težinom ili pretilošću — sustavni pregled literature s metaanalizom i metaregresijom

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Uvod: Sindrom policističnih jajnika (PCOS) najčešći je endokrinološki poremećaj u žena reproduktivne dobi. Cilj ovoga sustavnog pregleda s metaanalizom i metaregresijom jest usporediti učinak različitih lijekova koji povećavaju inzulinsku osjetljivost na metaboličke i reproduktivne ishode u žena s PCOS-om i prekomjernom tjelesnom težinom ili pretilošću.

Metode: Radi identificiranja studija objavljenih do 13. 11. 2023. pretražene su mrežne baze radova MEDLINE putem OVID-a, EMBASE, Clinicaltrials.gov i EudraCT. Uključni kriteriji za studije bile su dvostruko slijepe randomizirane kliničke studije koje su prikazale metaboličke ili reproduktivne ishode na ženama kojima je dijagnosticiran PCOS i indeks tjelesne mase (BMI) ≥ 25 kg/m2. Kao intervencija određena je primjena lijekova koji povećavaju inzulinsku osjetljivost, a za komparaciju su određeni ostali lijekovi ili placebo. Primarni ishodi bili su promjene početnog BMI-ja, razine glukoze u krvi natašte i učestalost menstruacija.

Rezultati: Devetnaest studija uključeno je u ovaj sustavni pregled. Metformin je imao najznačajniji učinak na razinu glukoze natašte i BMI. Lijekovi koji povećavaju inzulinsku osjetljivost značajno su smanjili razine glukoze natašte, BMI, razine inzulina u serumu natašte, HOMA-IR, globulin-vezač spolnih hormona (SHBG) i ukupni testosteron, no sa smanjenom razinom učinka. Nije bilo dostupno dovoljno podataka o učestalnosti menstruacije i o živorođenosti.

Zaključak: Rezultati upućuju na postojanje uloge lijekova koji smanjuju inzulinsku osjetljivost na povećanje metaboličkih i, premda u manjem opsegu, reproduktivni profil u ovih žena. Daljnja istraživanja trebaju utvrditi učinak tih lijekova na plodnost.

Ključne riječi: PCOS, lijekovi koji povećavaju inzulinsku osjetljivost, fertilitet, metaanaliza
Rad je u cijelosti objavljen dana 4. travnja 2024. u časopisu Obesity Reviews (doi: 10.1111/obr.13744).

S2 Impact of insulin sensitization on metabolic and fertility outcomes in women with polycystic ovary syndrome and overweight or obesity — A systematic review, meta-analysis, and meta-regression

Introduction: Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in reproductive-age women. This systematic review, meta-analysis, and meta-regression aims to compare the effect of insulin sensitizer pharmacotherapy on metabolic and reproductive outcomes in women with PCOS and overweight or obesity.

Methods: We searched online databases MEDLINE via OVID, EMBASE, Clinicaltrials.gov, and EudraCT for trials published from inception to November 13, 2023. Inclusion criteria were double-blind, randomized controlled trials in women diagnosed with PCOS, body mass index (BMI) ≥ 25 kg/m2, which reported metabolic or reproductive outcomes. The intervention was insulin sensitization pharmacotherapy versus placebo or other agents. The primary outcomes were changes from baseline BMI, fasting blood glucose, and menstrual frequency.

Results: Nineteen studies were included in this review. Metformin had the most significant effect on the fasting plasma glucose and body mass index. Insulin sensitizer pharmacotherapy significantly reduced fasting plasma glucose, body mass index, fasting serum insulin, HOMA-IR, sex hormone binding globulin, and total testosterone, but the effect size was small. There was a lack of menstrual frequency and live birth data.

Conclusion: The results indicate a role for insulin sensitizers in improving the metabolic and, to a lesser degree, reproductive profile in these women. Further research should examine insulin sensitizers´ effects on objective measures of fecundity.

Keywords: PCOS, insulin sensitization, fertility, meta-analysis
This paper was published on 4 April 2024 in Obesity Reviews (doi: 10.1111/obr.13744).

HIPOFIZA I NET

S3 Kad glavobolja nije samo glavobolja – prikaz slučaja

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Uvod: Apopleksija hipofize može biti po život opasno stanje koje nastaje kao posljedica krvarenja i/ili infarkta, tumorskim ili netumorskim procesom uvećane hipofize. Najčešće se prezentira iznenadnom glavoboljom povezanom s poremećajem vida ili raznim neurološkim simptomima[1]. Incidencija apopleksije hipofize u literaturi varira od 4% do 20%, a javlja se predominantno u muškaraca[2]. Apopleksije hipofize se češće javljaju u nefunkcionalnim nego u funkcionalnim adenomima, a oko 10% apoplektičkih epizoda događa se u nehipofiznim lezijama[4]. Apopleksija hipofize povezana je s nizom precipitirajućih čimbenika koji uključuju traumu glave, prethodne kirurške zahvate, trudnoću, lijekove (npr.antiagregacijske lijekove, antikoagulanse, agoniste dopamina, agoniste gonadotropina), endokrinološka ispitivanja[1]. Prikazat ćemo bolesnika s apopleksijom hipofize bez evidentiranog adenoma koji se prezentirao tipičnom kliničkom slikom, a na koju se nije posumnjalo u inicijalnom pregledu.

Prikaz slučaja: U 5. mjesecu 2020. godine, tada 63-godišnji bolesnik, do tada zdrav, pregledan je u OHBP zbog iznenadne, jake glavobolje zatiljno koja je nastupila 6 dana pred pregled, a bila je praćene mučninom i povraćanjem, te subfebrilitetom, vrtoglavicom te osjećajem nestabilnosti. Testiran je na COVID-19, pristigao negativan. Zbog umjereno povišenih markera upale i radiološki smanjene prozračnosti plućnog parenhima, pregledan je sa strane infektologa i ambulantno liječen kao upala pluća. Tada pregledan i sa strane neurologa, učinjen MSCT mozga na koji se nitko nije osvrnuo. Nakon provedene antibiotske terapije pacijent se i dalje žalio na izuzetnu slabost i iznemoglost. Ambulantno učinjeni nalazi hormona štitnjače ukazivali su na sekundarnu hipotireozu te je dogovorena dodatna obrada kroz endokrinološku dnevnu bolnicu. Učinjeni nalazi govorili su u prilog panhipopituitarizmu, dok je na MR hipofize viđen izrazito reduciran volumen adnohipofize koja se na postkontrastnim presjecima nije imbibirala kontrastom. Nakon uvida u inicijalni MSCT mozga, radiolog je bio mišljenja da se radi o stanju nakon apopleksije adenohipofize sa sada izrazito reduciranim parenhimom. Uvedena je supstitucijska terapija (hidrokortizon, levotiroksin, testosterone) nakon čega se pacijent u potpunosti klinički oporavio.

Rasprava: Naš se bolesnik prezentirao tipičnom kliničkom slikom koja je obzirom na period u kojem se javila (početak Covid-19 pandemije), bila u potpunosti zanemarena pa je liječenje usmjereno isključivo na početnu upalu pluća.

Zaključak: Iako je apopleksija hipofize rijetko stanje, potrebno je u određenim kliničkim stanjima posumnjati na njega obzirom da se smrtnost prema literaturi kreće između 1-5%, a da brza intervencija, bila ona kirurška ili konzervativna, može bolesniku spasiti život (1).

Ključne riječi: apopleksija hipofize, iznenadna glavobolja, panhipopituitarizam

Literatura: [1] Biagetti, B.; Simò, R. Pituitary Apoplexy: Risk Factors and Underlying Molecular Mechanisms. Int. J. Mol. Sci. 2022, 23, 8721.https://doi.org/10.3390/; [2] Muthukumar N. Pituitary Apoplexy: A Comprehensive Review. Neurol India 2020;68:S72-8; [3] Rajasekaran S, Vanderpump M, Baldeweg S, Drake W, Reddy N, Lanyon M et al. UK guidelines for the management of pituitary apoplexy. Clin Endocrinol (Oxf). 2011 Jan;74(1):9-20. doi: 10.1111/j.1365-2265.2010.03913.x; [4] Jho DH, Biller BMK, Agarwalla PK, Swearingen B. Pituitary apoplexy: Large surgical series with grading system. World Neurosurg 2014;82:781-90

S3 When a headache is not just a headache: a case report

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Introduction and aim: Pituitary apoplexy is a critical condition that arises when the hypertrophied pituitary gland undergoes infarction or hemorrhage, potentially due to a neoplasm or some underlying disorder. The predominant symptom is an abrupt headache followed by visual abnormalities or various neurological manifestations[1]. The prevalence of pituitary apoplexy in the literature ranges from 4% to 20%, primarily affecting males[2]. Pituitary apoplexy is more prevalent in non-functional adenomas compared to functional adenomas, with around 10% of apoplectic incidents arising from non-pituitary lesions [4]. Precipitating factors for pituitary apoplexy include head trauma, previous surgical procedures, pregnancy, medications (e.g., antiplatelet drugs, anticoagulants, dopamine agonists, gonadotropin agonists), and endocrinological tests[1]. We will exhibit a patient who presented with a typical clinical picture and pituitary apoplexy without a recorded adenoma, which was not suspected during the initial examination.

Case presentation: On May 5, 2020, a previously healthy 63-year-old patient was evaluated in the emergency department due to a sudden, severe headache at the occipital region that had manifested six days before the evaluation. The patient exhibited nausea, vomiting, mild fever, dizziness, and a sensation of instability. He tested negative for COVID-19. Owing to moderately raised inflammatory markers and radiologically diminished lung parenchyma transparency, he was evaluated by an infectious disease specialist and treated on an outpatient basis for pneumonia. He was subsequently examined by a neurologist, and an MSCT of the brain was conducted, which was not reviewed by anyone. The patient continued to experience severe fatigue and lethargy following the antibiotic therapy. After the outpatient thyroid hormone tests revealed secondary hypothyroidism, the endocrinology day hospital arranged for additional treatment. The examination indicated panhypopituitarism. An MRI of the pituitary gland indicated a significantly diminished volume of the adenohypophysis, and contrast was absent in the post-contrast sections. Upon reviewing the initial MSCT of the brain, the radiologist concluded that the condition was a result of an apoplexy of the adenohypophysis, resulting in an extremely reduced parenchyma. Substitution therapy (hydrocortisone, levothyroxine, testosterone) was implemented, resulting in the patient´s complete clinical recovery.

Discussion: Our patient had a typical clinical presentation, which was entirely disregarded due to the fact that it occurred at the inception of the Covid-19 pandemic. Consequently, the treatment was exclusively directed toward the initial pneumonia.

Conclusion: Despite the rarity of pituitary apoplexy, it is important to consider it in specific clinical situations. The literature indicates that the mortality rate is between 1-5%, and prompt intervention, whether surgical or conservative, can potentially save the patient's life[1].

Key terms: panhypopituitarism, sudden headache, pituitary apoplexy

Literature: [1] Biagetti, B.; Simò, R. Pituitary Apoplexy: Risk Factors and Underlying Molecular Mechanisms. Int. J. Mol. Sci. 2022, 23, 8721.https://doi.org/10.3390/ [2] Muthukumar N. Pituitary Apoplexy: A Comprehensive Review. Neurol India 2020;68:S72-8; [3] Rajasekaran S, Vanderpump M, Baldeweg S, Drake W, Reddy N, Lanyon M et al. UK guidelines for the management of pituitary apoplexy. Clin Endocrinol (Oxf). 2011 Jan;74(1):9-20. doi: 10.1111/j.1365-2265.2010.03913.x; [4] Jho DH, Biller BMK, Agarwalla PK, Swearingen B. Pituitary apoplexy: Large surgical series with grading system. World Neurosurg 2014;82:781-90

S4 Rezistentni prolaktinom — od optimizacije medikamentozne terapije do kirurškog pristupa

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Uvod: Prolaktinomi kao najčešći adenomi hipofize, dobro reagiraju na medikamentozno liječenje primjenom dopaminergičnih derivata ergolina. Primjenom kabergolina može se postići nomalizacija vrijednosti prolaktina u 80% slučajeva makroprolaktinoma te smanjenje tumorske mase za više od 50% u čak 55% slučaja. Međutim slučajevi makroprolaktinoma rezistentnih na primjenu ergot derivata predstavljaju velik dijagnostički i terapijski izazov u svakodnevnoj kliničkoj praksi. Cilj ovog prikaza slučaja je pokazati povoljan učinak kirurške resekcije makroprolaktinoma rezistentnog na medikamentoznu terapiju.

Prikaz slučaja: Prikazujemo bolesnicu u dobi od 50 godina koja je 2005. i 2007.g. imala dvije uredne trudnoće i poroda a u koje je od kraja 2013.g. (u dobi od 38 godina) prisutna oligomenoreja. Od 10/2013.g. primijećena je galaktoreja te je obradom utvrđena hiperprolaktinemija. MR-om hipofize inicijalno se prikazala dobro ograničena ovalna zona intenziteta tekućine promjera 14x10x13mm u području hipofize lijevo s minimalnim prijelazom na desnu stranu te blaži pomak infundibuluma. U 3/2014.g. započeto je liječenje bromokriptinom kojeg bolesnica nije dobro tolerirala te je isti zamijenjen za kabergolin. Obzirom na i dalje prisutne povišene vrijednosti prolaktina – 944 mIU/L (ref. do 557), u 3/2015g. povećana je doza kabergolina na 1.5mg 2 x tjedno. Kontrolni MR hipofize u 4/2015g. pokazao je inicijalnu regresivnu dinamiku veličine makroadenoma u odnosu na 10/2014.g., dimenzija 12,8x5,3x5,1mm te minimalnu devijaciju distalnog dijela infundibuluma hipofize. Klinički se pratilo poboljšanje stanja bolesnice – uspostavljeni su redovni menstrualni ciklusi uz izostanak galaktoreje. Nalaz fundusa i VP po Goldmanu bili su uredni. Kontrolnom radiološkom obradom pratila se stacionarna veličina makroadenoma (2016., 2017., 2018., 2019.) uz i dalje prisutnu hiperpolaktinemiju s tendencijom porasta serumskih vrijednosti (805,5 – 1568,6 mIU/L). U 8/2017.g. VP – formiranje lučnog skotoma desno. U 12/2017.g. UZV srca – bez valvulopatije. U 7/2019.g povećana je doza kabergolina na 1,5mg 3xtjedno te se unatoč tome pratila hiperprolaktinemija (879 – 2796 mIU/L) uz MR-om opisan stacionaran nalaz makroadenoma (2020., 2022., 2024.). Obzirom na isto, u 12/2024. učinjena je transsfenoidalna endoskopska adenomektomija nakon čega se bilježi uredna vrijednost prolaktina (215 mIU/L) no bolesnica je poslijeoperativno razvila AVP deficijenciju te je u 3/2025.g. planirana endokrinološka reevaluacija.

Rasprava: Riječ je o mladoj bolesnici s makroprolaktinomom u koje su primjenjene dvije linije medikamentozne terapije dopaminergičkim agonistima te se usprkos visokim dozama istih nije pratilo laboratorijsko niti radiološko poboljšanje. Obzirom na duži period primjene kabergolina periodično su učinjene reevaluacije te nije došlo do razvitka komplikacija. Bolesnica je prezentirana multidisciplinarnom timu liječnika te je preporučena kirurško liječenje – adnomektomija, a prema posljednjim preporukama liječenja makroprolaktinoma. Potonja metoda liječenja pokazala se uspješnom te se pratila rezolucija hiperprolaktinemije uz odstranjenje tumorske mase.

Zaključak: Značajan dijagnostički i terapijski izazov predstavljaju prolaktinomi rezistentni na dopaminergičke agoniste – dijagnostički treba razmotriti mogućnost malignog prolaktinoma i efekta mase na infundibulum, dok su terapijski iskorištene medikamentozne terapije. Cilj ovoga prikaza bio je skrenuti pažnju na mogućnost transsfenoidalne adenomektomije kao optimalnog liječenja makroprolaktinoma te razjašnjenja etiologije perzistentne hiperprolaktinemije kao i potaknuti na smanjenje kliničke inercije u svakodnevnoj kliničkoj praksi.

Ključne riječi: adenomektomija, ergot derivati, hipofiza, makroadenom, prolaktinom

Literatura: [1] **Raverot G, Burman P, McCormack A, Heaney A, Petersenn S, Popovic V i sur. The European Society of Endocrinology, European Society of Endocrinology Clinical Practice Guidelines for the management of aggressive pituitary tumours and carcinomas. Eur J Endocrinol. Volume 178, Issue 1, Jan 2018, Pages G1–G24.;** [2] **Molitch ME, Drummond J, Korbonits M, Feingold KR, Anawalt B, Blackman MR, i sur. Prolactinoma management. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000. 2022 Jan 6.;** [3] **Petersenn S, Fleseriu M, Casanueva FF i sur. Diagnosis and management of prolactin-secreting pituitary adenomas: a Pituitary Society international Consensus Statement. Nat Rev Endocrinol 19, 722–740 (2023).**

Resistant prolactinoma – from optimization of medical treatment to surgical approach

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Introduction: Prolactinomas respond well to medical treatment with dopaminergic derivates of ergoline. Using cabergoline, normalisation of prolactin values can be achieved in 80% of cases of macroprolactinoma and reduction of the tumor mass. However, cases of macroprolactinoma resistant to ergot derivates represent a great diagnostic and therapeutic challenge. The aim of this case report is to demonstrate the beneficial effect of surgical approach to macroprolactinoma resistant to medical treatment.

Case report: We present a 50-year-old patient who had two regular pregnancies and deliveries in 2005. and 2007. Since the end of 2013. (at the age of 38) oligomenorrhea was present. From 10/2013. galactorrhea was observed and hyperprolactinemia was determined. MRI of pituitary gland initially showed a well-limited oval zone of fluid intensity dimensions 14x10x13mm in the pituitary region on the left with a minimal transition to the right side and a mild shift of the infundibulum. In 3/2014. treatment with bromocriptine was started, which the patient did not tolerate, hence it was replaced by cabergoline. Considering the persistent hyperprolacinemia – 944 mIU/L (r. to 557), in 3/2015. the dose of cabergoline was increased to 1.5 mg twice a week. Control MRI in 4/2015. showed the initial regressive dynamics of the size of the macroadenoma, measuring 12.8x5.3x5.1 mm and minimal deviation of the distal part of the infundibulum. The improvement of the patient´s condition was observed – regular menstrual cycles were established with the absence of galactorrhea. The findings of the visual field was in order. The control radiological workup monitored the stationary size of the macroadenoma with persistent hyperprolactinemia and increasing tendency (805.5 – 1568.6 mIU/L). In 8/2017. visual field testing showed formation of an arcuate scotoma on the right. At 12/2017. echosonography did not show valvulopathy. At 7/2019. the dose of cabergoline was increased to 1.5 mg 3 times a week, and despite this, hyperprolactinemia (879 – 2796 mIU/L) was monitored with a stationary finding of macroadenoma described by MRI. Considering this, at 12/2024.g. a transsphenoidal endoscopic adenomectomy was performed, after which a normal prolactin value was recorded (215 mIU/L). Patient developed postoperatively AVP deficiency, and at 3/2025.g. endocrinological reevaluation is planned.

Discussion: We have presented a young patient with macroprolactinoma in whom two lines of medical therapy were applied. Despite high doses, no laboratory or radiological improvement was observed. Due to the longer period of cabergoline usage, periodic reevaluations were made. The patient was presented to a multidisciplinary team and surgical treatment was recommended, according to the latest recommendations for macroprolactinoma treatment. This method proved to be successful.
Conclusion: A significant diagnostic and therapeutic challenge is represented by prolactinoma resistant to dopaminergic agonists – diagnostically, the possibility of malignant prolactioma and mass effect on the infundibulum should be considered, while all the conservative methods were used. The aim of this case report was to draw attention to transsphenoidal adenomectomy as an optimal treatment for macroprolactinoma as well as to encourage the reduction of clinical inertia.

Keywords: adenomectomy, ergot derivates, macroadenoma, pituitary gland, prolactinoma

Literature: [1] Raverot G, Burman P, McCormack A, Heaney A, Petersenn S, Popovic V et al. The European Society of Endocrinology, European Society of Endocrinology Clinical Practice Guidelines for the management of aggressive pituitary tumours and carcinomas. Eur J Endocrinol. Volume 178, Issue 1, Jan 2018, Pages G1–G24.; [2] Molitch ME, Drummond J, Korbonits M, Feingold KR, Anawalt B, Blackman MR, et al. Prolactinoma management. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000. 2022 Jan 6.; [3] Petersenn S, Fleseriu M, Casanueva FF et al. Diagnosis and management of prolactin-secreting pituitary adenomas: a Pituitary Society international Consensus Statement. Nat Rev Endocrinol 19, 722–740 (2023).

S5 Prikaz slučaja: Izazovi u liječenju prolaktinoma

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Uvod s ciljem: Prolaktinomi su najčešći sekretorni adenomi hipofize. Klinička prezentacija posljedica je hiperprolaktinemije, odnosno veličine i invazivnosti samog tumora. Kada postoji diskrepancija između veličine tumora i blago povišenih razina prolaktina, preporučuje se mjeriti razinu prolaktina u razrjeđenju, kako bi se izbjegle lažno snižene vrijednosti uzrokovane laboratorijskim interferencijama. Preporučeno inicijalno liječenje je agonistima dopaminskih receptora, a drugi modaliteti, ovisno o veličini tumora i karakteristikama pacijenta, uključuju kirurško liječenje i zračenje. Cilj je ovog rada kroz prikaz slučaja potaknuti na diskusiju o poteškoćama prilikom postavljanja dijagnoze adenoma hipofize te o različitim modalitetima liječenja prolaktinoma i njihovom utjecaju na ishod.

Prikaz slučaja: Sedamdeset dvogodišnja pacijentica, s anamnezom arterijske hipertenzije, pretilosti, šećerne bolesti i hipotireoze, kod koje je ranije učinjena histerektomija s adneksektomijom zbog adenokarcinoma endometrija, javila se u hitnu službu zbog glavobolje uz ptozu desne vjeđe. Tada je prilikom inicijalne obrade učinjen CT mozga kojim se opisuje solidna tvorba u području selle turcica sa širenjem na desni kavernozni sinus. S obzirom na trombocitopeniju u inicijalnim laboratorijskim nalazima, hospitalizirana je na Odjel hematologije, gdje je postavljena dijagnoza imune trombocitopenija te započeta parenteralna kortikosteroidna terapija. Tijekom daljnje dijagnostičke obrade utvrđene su povišene vrijednosti prolaktina (2192 mU/l). Učinjen je MR mozga kojim se opisuje homogena solidna ekspanzivna tvoba u centralnom dijelu i desnoj polovini selle turcice, veličine 12x20x16 mm, radiomorfoloških karakteristika makroadenoma hipofize. Nastavljeno je liječenje metilprednizolonom uz koji se pratila normalizacija vrijednosti trombocita, uz pogoršanje vrijednosti glikemije, zbog čega je u terapiju uvedena intenzivirana inzulinska terapija. Pratila se perzistentna ptoza vjeđe. Bolesnica je zatim upućena u tercijarni centar, gdje su u daljnjoj dijagnostičkoj obradi izmjerene razine prolaktina u razrjeđenju, koje su bile unutar referentnih vrijednosti, te je postavljena indikacija za neurokirurški zahvat. Nakon uspješnog operativnog zahvata došlo je do potpunog oporavka neurološkog deficita, a naknadno pristigao nalaz patohistološke dijagnostike govorio je u korist prolaktinoma.

Rasprava: Brojna su stanja koja mogu utjecati na ispravno postavljenu dijagnozu hiperprolaktinemije, od kliničkih poput korištenja neuroleptičkih lijekova, adenoma koji luče hormon rasta ili TSH, do laboratorijskih artefakata, poput prozonskog učinka (engl. hook effect) i makroprolaktinemije. Preferirano inicijalno liječenje većine makroprolaktinoma, neovisno o postojanju simptoma hiperprolaktinemije, primjena je dopaminskih agonista, s obzirom na utjecaj koji imaju na smanjenje tumora i prevenciju daljnjeg rasta. Rezultati medikamentozne terapije, u smislu smanjenja veličine i stope

povrata, superiorni su u usporedbi s kirurškim liječenjem. Međutim, operativni zahvat indiciran je u pacijenata koji ne tolereriraju, odnosno onih koji su rezistentni na liječenje dopaminskim agonistima, kao i kod pacijentica koje planiraju trudnoću te pacijenata s apopleksijom ili likvorejom.

Zaključak: Individualne karakteristike pacijenta utječu na konačnu odluku o načinu liječenja. Biokemijske karakteristike (uredan nalaz prolaktina u razrjeđenju), uz izostanak simptoma hiperprolaktinemije i komorbiditete (trombocitopenija) u ovom su slučaju dvojako utjecali na izbor terapije u pacijentice kod koje se u daljnjem praćenju bilježio potpuni oporavak.

Ključne riječi: prolaktinom, hiperprolaktinemija, makroadenom, dopaminski agonisti

Literatura: [1] Melmed S, Auchus RJ, Goldfine AB, Rosen CJ, Kopp PA. Williams Textbook of Endocrinology. Elsevier Health Sciences; 2024.; [2] Tirosh A, Shimon I. Management of macroprolactinomas. Clinical Diabetes and Endocrinology [Internet]. 2015 Jul 20 [cited 2020 Feb 2];1(1). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5469196/#CR50; [3] Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, et al. Diagnosis and Treatment of Hyperprolactinemia: An Endocrine Society Clinical Practice Guideline. The Journal of Clinical Endocrinology & Metabolism [Internet]. 2011 Feb;96(2):273–88. Available from: https://academic.oup.com/jcem/article/96/2/273/2709487

S5 Case report: Challenges in the treatment of prolactinoma

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Introduction/objectives: Prolactinomas are the most common secretory pituitary adenomas. Clinical presentation is a result of hyperprolactinemia or tumor mass effect and invasion. When there is a discrepancy between tumor size and slightly elevated prolactin levels, serial dilution of serum samples is recommended to avoid falsely low prolactin values due to laboratory artifacts. Recommended initial treatment of prolactinoma is dopamine agonist therapy, and other modalities, depending on the tumor size and patient characteristics, include surgery and radiotherapy. This case report aims to encourage discussion about the exertion diagnosing pituitary adenoma and about various treatment options and their impact on the outcomes.

Case presentation: A seventy-two-year-old female patient with a history of arterial hypertension, obesity, diabetes, and hypothyroidism, who had earlier undergone hysterectomy with adnexectomy due to endometrial cancer, is admitted to the emergency room because of the headache with right eyelid ptosis. Initial workup included a brain CT scan, which showed solid mass in the sella turcica region, spreading to the cavernous sinus. Due to the thrombocytopenia in the initial laboratory results, the patient had been hospitalised in the Hematology department, where the immune thrombocytopenia was diagnosed, and parenteral corticosteroid therapy was initiated. Further evaluation revealed elevated prolactin levels (2192 mU/l). An MRI of the brain was performed and described a homogenous solid expansive lesion in the central and the right part of the sella turcica, measuring 12x20x16 mm, with radiomorphological characteristics of a pituitary macroadenoma. Methylprednisolone treatment was continued, causing worsening of glycemia, so intensive insulin therapy was started. Right ptosis continued. The patient was then referred to the tertiary referral centre. Further workup included serial dilution of serum samples, which showed prolactin levels within reference values, and the surgery indication had been set. After the successful surgical procedure, total recovery of the neurological deficit occurred, and the subsequently received pathohistological analysis report pointed to prolactinoma.

Discussion: Various conditions can affect correct diagnosis of hyperprolactinemia, from clinical, such as neuroleptic drugs, adenomas secreting growth hormone or TSH, to laboratory errors, such as "hook effect" and macroprolactinemia. Preferred initial treatment for most macroprolactinomas, regardless of the symptoms of hyperprolactinemia, is dopamine agonist therapy, considering its effect on the size of tumor and prevention of further growth. Pharmacological treatment effects on downsizing and preventing recurrence are superior compared to surgical treatment

outcomes. However, surgery is indicated in patients who do not tolerate or are dopamine agonist resistant, in patients planning pregnancy, and in patients with apoplexy or cerebrospinal fluid leak.

Conclusion: Individual patient characteristics influence the final decision for the treatment of choice. Biochemical characteristics (normal results of serum prolactin), as well as absence of hyperprolactinemia symptoms and comorbidities (thrombocytopenia), had an ambivalent effect on the treatment choice in the patient who had complete recovery in postoperative follow-up.

Keywords: prolactinoma, hyperprolactinemia, macroadenoma, dopamine agonist

Literature: [1] **Melmed S, Auchus RJ, Goldfine AB, Rosen CJ, Kopp PA. Williams Textbook of Endocrinology. Elsevier Health Sciences; 2024.;** [2] **Tirosh A, Shimon I. Management of macroprolactinomas. Clinical Diabetes and Endocrinology [Internet]. 2015 Jul 20 [cited 2020 Feb 2];1(1). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5469196/#CR50;** [3] **Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, et al. Diagnosis and Treatment of Hyperprolactinemia: An Endocrine Society Clinical Practice Guideline. The Journal of Clinical Endocrinology & Metabolism [Internet]. 2011 Feb;96(2):273–88. Available from: https://academic.oup.com/jcem/article/96/2/273/2709487**

S6 Izazovi u liječenju gigantskih makroadenoma hipofize

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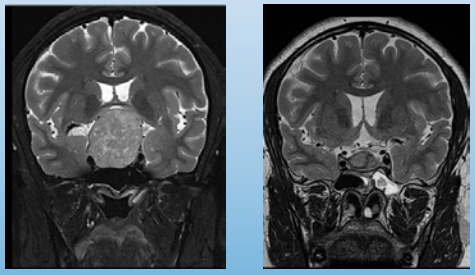
Uvod s ciljem: Adenomi hipofize su većinom benigni, monoklonalni tumori podrijetlom stanica adenohipofize koji čine 10-20% svih intrakranijskih tumora (1). Prema veličini dijelimo ih na mikroadenome (<1 cm), makroadenome (≥1 cm) i gigantske makroadenome (≥4 cm), a ovisno o funkcionalnom statusu na funkcionalne i nefunkcionalne. Prva linija liječenja neufunkcionalnih makroadenoma je kirurška. Obzirom na nemogućnost postizanja totalne resekcije tumora jednom operacijom te veći rizik postoperativnih komplikacija kod gigantskih adenoma prednost se daje operaciji u dva akta.

Prikaz slučaja: Bolesnik u dobi od 36 godina klinički se je prezentirao smetnjama vida i erektilnom disfunkcijom unatrag godinu dana. Hitni CT mozga je prikazao unutar sele turcike hiperdenznu tvorbu vel. 37x37x39 mm zbog čega je ciljano učinjen MR hipofize kojim je potvrđeno da ekspanzivna tvorba promjera 40 mm odgovara makroadenomu hipofize (slika 1.). Endokrinološkom obradom utvrđeno je kako se radi o nefunkcionalnom makroadenomu sa ispadom funkcije tireotropnih i gonadotropnih stanica. Kod bolesnika je učinjena endoskopska transsfenoidalna adenomektomija makroadenoma hipofize, a PHD nalaz je odgovarao Pit-NET gonadtropinomu, Ki-67 <3%. Na prvoj postoperativnoj kontroli nakon 3 mjeseca došlo je do spuštanja tumorske mase vel. 14x21x13mm (slika 2.) koja supraselarno više nije u kontaktu s optičkom hijazmom što je klinički objektivizirano oporavkom vida. Uvidom u funkciju stanica adenohipofize i dalje se prati sekundarni hipogonadizam te je uvedena nadomjesna terapija testosteronom. Kod bolesnika je indicirana druga operacija s ciljem totalne resekcije tumora.



Slika 1. Preoperativni MR-hipofize u T2 mjernom vremenu s prikazom gigantskog makroadenoma s pritiskom na optičku hijazmu.

Slika 2. Postoperativni MR-hipofize 3 mjeseca nakon operacije u T2 mjernom vremenu s prikazom tumorske rezidue.

Rasprava: U slučaju gigantskih makroadenoma hipofize sa simptomima kompresivnog učinka na okolne neurovaskularne strukture, izuzev makroprolaktinoma, prvi izbor liječenja je kirurški. Dva su moguća kirurška pristupa transsfenoidalno i transkranijski. U većini slučajeva zbog veličine makroadenoma nije moguće jednom operacijom postići totalnu resekciju tumora, a rizik za intraoperativno masivno krvarenje je velik kao i rizik razvoja postoperativnih komplikacija (2.) stoga se najčešće odlučujemo na operaciju u dva akta kao što je u našem prikazu slučaja.

Zaključak: Cilj ovog prikaza je naglasiti važnosti multidisciplinarnog pristupa kod liječenja bolesnika s gigantskim makroadenomom hipofize te dati prednost operaciji u dva akta s ciljem postizanja totalne ili subtotalne resekcije tumora, a sa znatno manjim postoperativnim komplikacija kao i boljom kvalitetom života bolesnika.

Ključne riječi: gigantski makroadenom, hipofiza, trannsfenoidalna operacija, operacija u dva akta

Literatura: [1] Drummond JB, Ribeiro-Oliveira A Jr., Soares BS. Non-FunctioningPituitaryAdenomas. [Updated 2022 Oct 12]. In: Feingold KR, Anawalt B, Blackman MR, etal., editors. Endotext [Internet]. SouthDartmouth (MA): MDText.com, Inc.; 2000-. Availablefrom: https://www.ncbi.nlm.nih.gov/books/NBK534880/
[2] Lei Mou, Jun Qin, Junrong Lei, Zhiming Chen, Jun Liu, ChiFeng, StagedSurgicalTreatmentoftheGiantPituitaryNeuroendocrineTumors, World Neurosurgery, Volume 192, 2024, Pages e12-e19, ISSN 1878-8750, https://doi.org/10.1016/j.wneu.2024.06.069.

S6 Challenges in the management of giant pituitary macroadenomas

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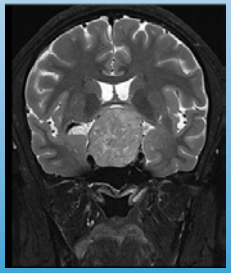
Introduction with aim: Pituitary adenomas are mostly benign, monoclonal tumors originating from the cells of the adenohypophysis, accounting for 10-20% of all intracranial tumors (1). Based on size, they are classified into microadenomas (<1 cm), macroadenomas (≥1 cm), and giant macroadenomas (≥4 cm), while based on functional status, they are divided into functional and non-functional tumors. The first line treatment for non-functional macroadenomas is surgery. Due to the inability to achieve total tumor resection in a single surgery and the increased risk of postoperative complications with giant adenomas, a two-stage surgical approach is preferred.

Case report: A 36-year-old male patient presented clinically with visual disturbances and erectile dysfunction for the past year. An emergency brain CT scan revealed a hyperdense mass within the sella turcica measuring 37x37x39 mm, prompting a targeted pituitary MRI, which confirmed an expansile mass with a diameter of 40 mm consistent with a pituitary macroadenoma (Image 1). Endocrinological evaluation showed that the mass was a non-functional macroadenoma with impaired function of thyrotropic and gonadotropic cells. The patient underwent endoscopic transsphenoidal adenomectomy for the pituitary macroadenoma, and the histopathological report confirmed a Pit-NET gonadotropinoma, with Ki-67 <3%. On the first postoperative follow-up, three months later, there was a reduction in the tumor mass to 14x21x13 mm (Image 2), and the mass was no longer in contact with the optic chiasm, which was clinically confirmed by the restoration of vision. Evaluation of the pituitary cell function continued to show secondary hypogonadism, and testosterone replacement therapy was initiated. A second surgery has been indicated for the patient with the goal of total tumor resection.



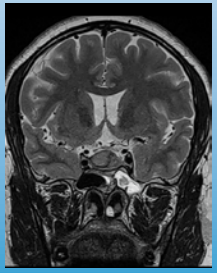


Image 1. Preoperative pituitary MRI in T2-weighted imaging showing a giant macroadenoma compressing the optic chiasm.

Image 2. Postoperative pituitary MRI, 3 months after surgery, in T2-weighted imaging showing the residual tumor.

Discussion: In the case of giant pituitary macroadenomas with symptoms of compressive effects on surrounding neurovascular structures, excluding macroprolactinomas, the first choice of treatment is surgical. Two surgical approaches are possible: transsphenoidal and transcranial. In most cases, due to the size of the macroadenoma, achieving total tumor resectionin a single surgery is not feasible, and the risk of massive intraoperative bleeding is high, as well as the risk of postoperative complications (2). Therefore, a two-stage surgical approach, as in our case presentation, is most commonly chosen. Conclusion: The aim of this case report is to emphasize the importance of a multidisciplinary approach in the treatment of patients with giant pituitary macroadenomas and to advocate for a two-stage surgical approach aimed at achieving total or subtotal tumor resection, with significantly fewer postoperative complications and improved quality of life for the patient.

Keywords: giant macroadenoma, pituitary gland, transsphenoidal surgery, two-stage surgery

Literature: [1] Drummond JB, Ribeiro-Oliveira A Jr., Soares BS. Non-FunctioningPituitaryAdenomas. [Updated 2022 Oct 12]. In: Feingold KR, Anawalt B, Blackman MR, etal., editors. Endotext [Internet]. SouthDartmouth (MA): MDText.com, Inc.; 2000-. Availablefrom: https://www.ncbi.nlm.nih.gov/books/NBK534880/; [2] Lei Mou, Jun Qin, Junrong Lei, Zhiming Chen, Jun Liu, ChiFeng, StagedSurgicalTreatmentoftheGiantPituitaryNeuroendocrineTumors, World Neurosurgery, Volume 192, 2024, Pages e12-e19, ISSN 1878-8750, https://doi.org/10.1016/j.wneu.2024.06.069.

S7 Autoimuna hemolitička anemija u bolesnice s metastatskim dobro diferenciranim neuroendokrinim tumorom želuca u sklopu MEN 4 sindroma

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Uvod: Autoimuna hemolitička anemija je rijetka bolest imunosnog sustava koju karakterizira hemoliza vlastitih eritrocita uzrokovana autoprotutijelima i/ili aktiviranim komponentama komplementa te se može javiti kao paraneoplastični sindrom kod hematoloških bolesti, ali i solidnih tumora. Prikazali smo bolesnicu s metastatskim NET-om želuca te prisutnim drugim sekvelama sindroma multiple endokrine neoplazije (MEN) kod koje je došlo do razvoja autoimune hemolitičke anemije kao paraneoplastičnog poremećaja.

Prikaz slučaja: Kod bolesnice je 2020. godine učinjena totalna gastrektomija zbog dobro diferenciranog neuroendokrinog tumora želuca gradusa 2 (Ki67 5%) sa lokalno pozitivnim limfnim čvorovima. Zbog suspektnog patološkog nakupljanja radiofarmaka na scintigrafiji somatostatinskih receptora dodatno je učinjen PET/CT s galij 68 DOTATATE u 9/2022 na kojem su se prikazivale dvije tumorske tvorbe u hilusu desnog pluća, infiltrati u gornjem režnju desnog pluća s patološkim metabolizmom kao i mekotkivna tvorba u medijastinumu. Pulmološkom obradom utvrđeno je da se radi o metastazama neuroendokrinog tumora želuca. Zbog razvoja kliničke slike ikterusa i pozitivnog direktnog antiglobulinskog testa utvrđena je autoimuna hemolitička anemija te je započeta kortikosteroidna terapija prema preporuci hematologu. Dodatnom dijagnostičkom obradom kod bolesnice je utvrđen primarni hiperparatireoidizam i nefunkcionalni mikroadenom hipofize. Zbog prisutnih sekvela koje upućuju na sindrom MEN 1 provedeno je gensko testiranje koje je bilo negativno. Kod bolesnice je započeto liječenje metastatskog neuroendokrinog tumora želuca G2 dugodjelujućim oktreotidom. Uz ranije započetu kortikosteroidnu terapiju kod bolesnice je postignuta remisija autoimune hemolitičke anemije.

Rasprava: Autoimuna hemolitička anemija (AIHA) može se javiti u bolesnika s hematološkim bolestima, ali i zloćudnim solidnim tumorima kao rijedak paraneoplastični sindrom. Nije razjašnjen patofiziološki mehanizam koji dovodi do njenog nastanka, ali se pretpostavlja kako dolazi do stvaranja protutijela na tumorske antigene koji potom križnom reakcijom oštećuju eritrocitne antigene. AIHA se može javiti kao prva prezentacija tumora te može biti i znak recidiva tumora nakon provedenog liječenja. Prikazali smo bolesnicu s metastatskim NET-om G2 želuca kod koje je došlo do nastanka autoimune hemolitičke anemije nakon provedenog kirurškog liječenja NET-a, u trenutku

razvoja metastatske bolesti (metastaze u plućnom parenhimu i medijastinalnim limfnim čvorovima). Zanimljivo je kako je bolesnica imala sve sekevele MEN 1 sindroma koji genskim testiranjem nije potvrđen. S obzirom na navedeno kod bolesnice smo posumnjali na MEN 4 sindrom, rijedak genski poremećaj, koji ima isti fenotipski spektar kao MEN1, ali je u podlozi mutacija gena CDKN1B koju nije moguće odrediti u Republici Hrvatskoj.

Zaključak: Do sad u literaturi nije opisan slučaj razvoja AIHA-e kod bolesnika s metastatskim dobro diferenciranim NET-om želuca. Kod naše bolesnice do razvoja AIHA-e je došlo u trenutku diseminacije neuroendokrinog tumora. Iz navedenog možemo zaključiti kako pojava AIHA-e nakon kirurškog liječenja neuroendokrinog tumora želuca može ukazivati na recidiv ili progresiju bolesti. AIHA može biti jedna od sekvela sindroma MEN 4.

Ključne riječi: autoimuna hemolitička anemija, dobro diferencirani neuroendokrini tumor želuca, MEN 4 sindrom

Literatura: [1] Puthenparambil J, Lechner K, Kornek G. Autoimmune hemolytic anemia as a paraneoplastic phenomenon in solid tumors: A critical analysis of 52 cases reported in the literature. Wien Klin Wochenschr. 2010;122(7-8):229-36.; [2] Papakonstantinou IP, Karakousis ND, Andreadis EA. Gastric neuroendocrine tumour, atrophic gastritis and autoimmune haemolytic anaemia: a case report and review. Scott Med J.2019 ;64(4):154-58.; [3] Sreedhar A, Nair R, Scialla W. Paraneoplastic Auto-immune Hemolytic Anemia: An Unusual Sequela of Enteric Duplication Cyst. Anticancer Research. 2018, 38 (1) 509-12.

S7 Autoimmune hemolytic anemia in a patient with metastatic well-differentiated gastric neuroendocrine tumor as part of MEN 4 syndrome

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Introduction: Autoimmune hemolytic anemia (AIHA) is a rare disease of the immune system characterized by hemolysis of erythrocytes caused by autoantibodies and/or activated complement components and can occur as a paraneoplastic syndrome in hematological diseases, but also in solid tumors. We presented a patient with metastatic well-differentiated gastric NET and other sequels of multiple endocrine neoplasia (MEN) syndrome, who developed AIHA as a paraneoplastic disorder.

Case report: In 2020, the patient underwent a total gastrectomy due to a well-differentiated gastric neuroendocrine tumor grade 2 (Ki67 5%) with locally positive lymph nodes. Due to the suspected pathological accumulation of radiopharmaceuticals on the octreoscan, a PET/CT with gallium 68 DOTATATE was performed in 9/2022 and revealed metastases in the hilum of the right lung, in the upper lobe of the right lung and mediastinal lymphadenopathy. Bronchoscopy was done and pathohistological analysis revealed metastases of well-differentiated gastric neuroendocrine tumor. Due to the development of icterus and a positive direct antiglobulin test, AIHA was established and corticosteroid therapy was recommended according to the hematologist. Additional diagnostic workup revealed primary hyperparathyroidism and non-functional pituitary microadenoma. Due to the presence of sequels associated with syndrome of MEN 1, genetic testing was performed but the result was negative. The patient was treated with long-acting octreotide for metastatic G2 gastric neuroendocrine tumor. With previously started corticosteroid therapy, the patient achieved remission of autoimmune hemolytic anemia.

Discussion: Autoimmune hemolytic anemia (AIHA) can occur in patients with hematological diseases as well as in malignant solid tumors as a rare paraneoplastic syndrome. The pathophysiological mechanism that leads to its occurrence has not been clarified, but it is assumed that antibodies against tumor antigens cross-react with erythrocyte antigens and cause hemolysis. AIHA can occur as the first presentation of a tumor and can also be a sign of tumor recurrence after treatment. We presented a patient with metastatic well- differentiated gastric NET who developed autoimmune hemolytic anemia after surgical treatment, at the time of the presentation of metastatic disease. Our patient had all the sequels of MEN 1 syndrome but because of the negative genetic testing we suspected on MEN 4 syndrome which is a rare genetic disorder with the same phenotypic spectrum as MEN1, but is caused by mutation of the CDKN1B gene, which

cannot be determined in the Republic of Croatia.
Conclusion: According to previous literature no case of AIHA in a patient with metastatic well-differentiated gastric neuroendocrine tumor has been recorded. In our patient the development of AIHA occurred at the time of metastatic disease. The appearance of AIHA after surgical treatment of a gastric neuroendocrine tumor can indicate a relapse or progression of the disease. AIHA can be one of the sequelae of MEN 4 syndrome.
Key words: autoimmune hemolytic anemia, well-differentiated gastric neuroendocrine tumor, MEN 4 syndrome

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S8 Od traumatske povrede glave do hipopituitarizma: prikaz slučaja

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Uvod: Traumatska povreda glave predstavlja po život opasno stanje koje godišnje pogađa oko 70 miliona ljudi. Posttraumatski hipopituitarizam se javlja u do 32% slučajeva i često protiče neprepoznat; funkcija hipofize se oporavi kod velikog broja ovih pacijenata.

Prikaz slučaja: Pacijent star 38 godina je zadobio traumatsku povredu glave kao vozač motocikla. Po prijemu je imao Glasgow koma skor 6 i zahtevao je intubaciju. Radiološkom dijagnostikom je utvrđen Le Fort III tip preloma, fraktura parijetalne kosti, multipli prelomi rebara i torakalnih pršljenova, suarahnoidalna i subduralna hemoragija, i edem mozga. U laboratorijskim nalazima je uočena hiperglikemija, patološki hepatogram, i povišene vrednosti inflamatornih parametara, dok su ostali rezultati bili neupadljivi. Iz medicinske istorije je dobijen podatak da se pacijent leči od tipa 2 šećerne bolesti. U danima nakon hospitalizacije, pacijent je zahtevao vazoaktivnu potporu usled hemodinamske nestabilnosti. Povrede glave su lečene konzervativno sa potpunom rezolucijom intrakranijalne hemoragije, dok je kraniofacijalna disjunkcija tretirana operativno. U daljem toku lečenja, perzistentna hemodinamska nestabilnost, nejatrogena hipoglikemija i neurološki deficit su podstakli endokrinološku evaluaciju kojom je dijagnostikovan panhipopituitarizam. Započeta je supstituciona terapija glukokortikoidima i levotiroksinom što je rezultiralo rapidnim kliničkim poboljšanjem. Magnetna rezonanca selarne regije je bila bez osobenosti. Na ambulantnoj kontroli dve godine nakon povrede perzistirao je ispad i u somatotropnoj funkciji, te je započeta supstituciona terapija hormonom rasta.

Zaključak: Traumatska povreda glave zahteva multidisciplinarni pristup u lečenju u koje mora biti uključen i endokrinolog. Ovi pacijenti zahtevaju strpljivo višegodišnje praćenje od strane endokrinologa.

Ključne reči: traumatska povreda glave, hipopituitarizam, pituitarna žlezda

Literatura: [1] Haarbauer-Krupa J, Pugh MJ, Prager EM, Harmon N, Wolfe J, Yaffe K. Epidemiology of Chronic Effects of Traumatic Brain Injury. J Neurotrauma. 2021 Dec;38(23):3235-3247. doi: 10.1089/neu.2021.0062. Epub 2021 Aug 17. PMID: 33947273; PMCID: PMC9122127.; [2] Gasco V, Cambria V, Bioletto F, Ghigo E, Grottoli S. Traumatic Brain Injury as Frequent Cause of Hypopituitarism and Growth Hormone Deficiency: Epidemiology, Diagnosis, and Treatment. Front Endocrinol (Lausanne). 2021 Mar 15;12:634415. doi: 10.3389/fendo.2021.634415. PMID: 33790864; PMCID: PMC8005917. [3] Tanriverdi F, Ulutabanca H, Unluhizarci K, Selcuklu A, Casanueva FF, Kelestimur F. Three years prospective investigation of anterior pituitary function after traumatic brain injury: a pilot study. Clin Endocrinol (Oxf). 2008;68(4):573-9.

S8 From traumatic brain injury to hypopituitarism: a case report

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Background: Traumatic brain injury is a life-threatening condition which affects around 70 million people annually. Post-traumatic hypopituitarism occurs in up to 32% of cases, often remaining unrecognised; it resolves in the majority of these patients.

Case summary: We report a case of a 38-year-old male who was hospitalised after sustaining a traumatic brain injury while riding a motorcycle. Upon admission, the patient had a Glasgow coma score of 6 requiring intubation. Imaging studies revealed Le Fort III, parietal bone fracture, multiple rib and thoracic vertebrae fractures, subarachnoid and subdural haemorrhage, and brain oedema. Laboratory tests revealed hyperglycaemia, abnormal liver function tests, and elevated inflammatory parameters, while the rest of the results were unremarkable. The patient had a history of type 2 diabetes. In the following days, due to hemodynamic instability, the patient required vasoactive support. Brain injuries were managed conservatively with a complete resolution of intracranial haemorrhage, while the craniofacial disjunction required surgical treatment. During further treatment, persistent hemodynamic instability, non-iatrogenic hypoglycemia and neurological impairment prompted an endocrinological evaluation, revealing panhypopituitarism. Glucocorticoid and levothyroxine replacement therapy was initiated leading to rapid clinical improvement. Pituitary magnetic resonance imaging was unremarkable. At the two-year follow-up visit, no improvement in the somatotropic axis was observed, thus growth hormone replacement therapy was also initiated.

Conclusion: Traumatic brain injury demands a multidisciplinary approach with an endocrinologist involved. These patients require careful endocrinological follow-up over several years post-injury.

Keywords: traumatic brain injury, hypopituitarism, pituitary gland

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NADBUBREŽNA ŽLIJEZDA

S9 Optimizacija protokola za uzorkovanje adrenalnih vena u dijagnostici primarnog hiperaldosteronizma — *More Than Meets the Eye*

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Uvod i cilj: Primarni hiperaldosteronizam (PA) najčešći je uzrok sekundarne hipertenzije. Dijagnosticira se u 5-20 % bolesnika s hipertenzijom, osobito u bolescnika s teškom i terapijski rezistentnom hipertenzijom. Jednostrana bolest uspješno se liječi adrenalektomijom, dok se obostrana bolest liječi medikamentozno, odnosno antagonistima mineralokortikoidnih receptora. Najvažnija metoda za razlikovanje podtipova je uzorkovanje adrenalnih vena (AVS).

Prikaz slučaja: Prikazan je slučaj 38-godišnjeg muškog bolesnika kojem je prije 5 godina dijagnosticirana arterijska hipertenzija, bez učinjenog probira na sekundarnu hipertenziju. Bolesnik se javio u hitnu službu s bolovima u prsima i povišenim vrijednostima arterijskog tlaka (200/120 mmHg). Nakon prijema u bolnicu, korigirana je antihipertenzivna terapija – liječen je s četiri antihipertenziva, ali vrijednosti arterijskog tlaka i dalje su bile nezadovoljavajuće. U laboratorijskim nalazima pratila se hipokalemija, s najnižom zabilježenom razinom kalija od 3,3 mmol/L. S obzirom na navedeno, posumnjalo se na sekundarnu hipertenziju, a najizglednija dijagnoza bila je PA. Provedeno je testiranje s određivanjem koncentracije direktnog renina (DRC), koncentracije aldosterona u plazmi (PAC) te omjera aldosteron/renin (ARR). Unatoč hipokalemiji, DRC je bio suprimiran (1,7 mIU/L), dok su PAC i ARR bili povišeni, 665 pmol/L i 391. MRI abdomena pokazao je blago nespecifično naglašeniji medijalni krak desne nadbubrežne žlijezde debljine do 6 mm. Nadalje, kao potvrdni test proveden je test opterećenja fiziološkom otopinom. Nakon 4 sata PAC nije bio suprimiran (407 pmol/L), što je u skladu s dijagnozom PA. Budući da sada imamo posvećenog interventnog radiologa, odlučili smo se po prvi put u našoj ustanovi učiniti AVS. AVS je proveden uz stimulaciju ACTH 250 µg koji je primijenjen kao kontinuirana infuzija započeta 30 minuta prije uzorkovanja i nastavljena tijekom postupka brzinom od 50 µg/sat. Indeks selektivnosti (SI), definiran kao omjer koncentracije kortizola u adrenalnoj veni i u donjoj šupljoj veni, iznosio je 6 za lijevu adrenalnu venu, ali za desnu adrenalnu venu SI je bio < 3, što ukazuje na neuspješnu kateterizaciju. Uz primjenu trenutne terapije, bolesnik ima stabilne razine kalija, a arterijski tlak je dobro reguliran, stoga je planiran ponovni AVS za tri tjedna.

Rasprava: Iako CT i MRI mogu pomoći u otkrivanju adrenalnih tumora, AVS ostaje zlatni standard za razlikovanje jednostranog od obostranog PA. Kateterizacija desne adrenalne

vene najzahtjevniji je dio AVS-a i glavni uzrok neuspjeha postupka, s uspješnošću od samo 70-80 % u iskusnim centrima. Primjena AVS-a kod bolesnika mlađih od 40 godina predmet je rasprave, no novije studije preporučuju ga kada je dostupan. Još jedno pitanje je treba li koristiti stimulaciju ACTH-om, budući da trenutne smjernice ne daju jasne preporuke. Neke studije predlažu provođenje AVS-a prije i nakon stimulacije ACTH-om, jer svaka metoda pruža komplementarne dijagnostičke informacije – stimulacija povećava uspješnost uzorkovanja, dok nestimulirano uzorkovanje poboljšava točnost lateralizacije, olakšavajući odluku o daljnjem liječenju.

Zaključak: Prepoznavanje i probir za PA kod bolesnika s hipertenzijom i povezanim čimbenicima rizika od velike su važnosti. Ako u obzir dolazi kirurško liječenje PA, potrebno je provesti AVS. Međutim, postupak je tehnički zahtjevan, a aspekti poput optimalnih kriterija za odabir bolesnika te metoda izvođenja i interpretacije AVS-a i dalje su predmet rasprave. Unatoč tim izazovima, AVS ostaje najpouzdaniji test za određivanje lateralizacije, uz kontinuirane napretke usmjerene na poboljšanje njegove učinkovitosti za bolesnike.

Ključne riječi: uzorkovanje adrenalnih vena, primarni hiperaldosteronizam, sekundarna hipertenzija

Literatura: [1] **Faconti L, Kulkarni S, Delles C, Kapil V, Lewis P, Glover M, et al. Diagnosis and management of primary hyperaldosteronism in patients with hypertension: a practical approach endorsed by the British and Irish Hypertension Society. J Hum Hypertens. 2024 Jan;38(1):8-18. doi: 10.1038/s41371-023-00875-1.;** [2] **Wolley M, Thuzar M, Stowasser M. Controversies and advances in adrenal venous sampling in the diagnostic workup of primary aldosteronism. Best Pract Res Clin Endocrinol Metab. 2020 May;34(3):101400. doi: 10.1016/j.beem.2020.101400. ;** [3] **Quencer KB, Singh A, Sharma A. Best Practices: Indications and Procedural Controversies of Adrenal Vein Sampling for Primary Aldosteronism. AJR Am J Roentgenol. 2023 Feb;220(2):190-200. doi: 10.2214/AJR.22.27692.;** [4] **Kocjan T, Jensterle M, Vidmar G, Vrckovnik R, Berden P, Stankovic M. Adrenal vein sampling for primary aldosteronism: a 15-year national referral center experience. Radiol Oncol. 2020 Aug 5;54(4):409-418. doi: 10.2478/raon-2020-0052.;** [5] **Hu J, Chen J, Cheng Q, Jing Y, Yang J, Du Z, et al. Comparison of Bolus and Continuous Infusion of Adrenocorticotropic Hormone During Adrenal Vein Sampling. Front Endocrinol (Lausanne). 2021 Nov 26;12:784706. doi: 10.3389/fendo.2021.784706.**

S9 Optimization of Adrenal Vein Sampling Protocol in the Diagnosis of Primary Hyperaldosteronism - More Than Meets the Eye

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Introduction and aim: Primary hyperaldosteronism (PA) is the most common cause of secondary hypertension. It is diagnosed in 5-20% of patients with hypertension, especially in severe and treatment-resistant cases. Unilateral disease can be successfully treated with adrenalectomy, while bilateral disease is treated medically with mineralocorticoid receptor antagonists. The most important method for differentiating the subtypes is adrenal vein sampling (AVS).

Case report: We present a case of a 38-year old male patient who was diagnosed with arterial hypertension 5 years ago, without having been screened for secondary hypertension. The patient was presented to the emergency room with chest pain and high BP (200/120 mmHg). After the patient was admitted to hospital, the antihypertensive therapy was modified – he was treated with four antihypertensive drugs, but BP levels remained suboptimal. Laboratory tests consistently showed hypokalemia, with the lowest potassium level recorded at 3.3 mmol/L. Considering above mentioned, secondary hypertension was suspected with PA being the most likely diagnosis. Case-detection testing was performed with the measurement of direct renin concentration (DRC), plasma aldosterone concentration (PAC) and aldosterone/renin ratio (ARR). Despite hypokalemia, DRC was suppressed 1.7 mIU/L, while PAC and ARR were elevated, 665 pmol/L and 391 respectively. Abdominal MRI showed a mildly nonspecifically prominent medial limb of the right adrenal gland, measuring up to 6 mm in thickness. Furthermore, the saline infusion test was performed as confirmatory test. After 4 hours PAC was not suppressed 407 pmol/L which is consistent with PA. We decided to perform AVS for the first time in our institution, as we now have a dedicated radiologist. AVS with ACTH 250 mcg stimulation was conducted. ACTH was administered as continuous infusion which was started 30 minutes before sampling and continued throughout the procedure at 50 mcg/hr. The selectivity index (SI), defined as the ratio of the plasma cortisol concentration (PCC) in adrenal vein to that in the inferior vena cava, in the left adrenal vein was 6, but in the right adrenal vein SI was < 3 which indicated unsuccessful cannulation. The patient's potassium levels are stable on the current medication regimen and BP is well regulated, so repeated AVS is planned in three weeks.

Discussion: Although CT and MRI can help detect adrenal masses, AVS remains the gold standard for distinguishing unilateral from bilateral PA. Right adrenal vein cannulation is the most challenging part of AVS and the main cause of procedure failure, with a success rate of only 70–80% in experienced centers. The use of AVS in patients under 40 is debated, but recent studies recommend it when available. Another concern is whether to use ACTH stimulation, as current guidelines provide no clear recommendations. Some studies suggest performing AVS both before and after ACTH stimulation, as each offers complementary diagnostic value – stimulation improves sampling success, while unstimulated sampling enhances lateralization accuracy, aiding treatment decisions. Conclusion: Detection and screening for PA in hypertensive patients with associated risk factors is very important. If surgical treatment is being considered, AVS should be performed. However, the procedure is technically demanding, and aspects such as the optimal criteria for patient selection and the methods for performing and interpreting AVS remain controversial. Despite these challenges, AVS remains the most reliable test for determining lateralization, with continued advances aimed at improving its effectiveness for patients.

Key words: adrenal vein sampling, primary hyperaldosteronism, secondary hypertension

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S10 Adrenokortikalni onkocitom — prikaz slučaja

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Uvod s ciljem: Cilj ovog rada je bio prikaz rijetkog slučaja adrenokortikalnog onkocitoma. Prikaz slučaja: Pacijentici staroj 27 godina na ultrazvučnom pregledu abdomena 2019. godine slučajno je otkrivena tvorba lijeve nadbubrežne žlijezde. Učinjena je magnetska rezonancija (MR) abdomena koja je opisivala "adenom" lijeve nadbubrežne žlijezde dimenzija 25x22mm. Laboratorijski nalazi su isključili hormonski aktivan tumor. Zaključeno je da se radi o afunkcionalnom adenomu. 2023. godine na kompjutoriziranoj tomografiji (CT) abdomena opisan je tumor lijeve nadbubrežne žlijezde dimenzija 55x35 mm, koji nije zadovoljavao morfološke kriterije za adenom. Diferencijalno dijagnostički dolazio je u obzir feokromocitom. Kontrolni MR abdomena je potvrdio da tumor ne odgovara adenomu. Pacijentica je bila bez simptoma, bez znakova hiperkorticizma i hirzutizma. Nalazi metanefrina i normetanefrina su bili unutar referentnih intervala, što je isključivalo feokromocitom: metanefrin 638 nmol/24 h (RI 0-1300 nmol/24 h), normetanefrin 1014 nmol/24 h (RI 0-2800 nmol/24 h). U ponovljenoj laboratorijskoj obradi nađene su povišene vrijednosti adrenalnih androgena i snižena razina estradiola: DHEAS 23,0 µmol/L, androstendion 13,2 nmol/L, estradiol <55 pmol/L. Nije bilo moguće isključiti autonomno lučenje kortizola; u produženom testu supresije od 48 sati nije postignuta odgovarajuća supresija kortizola: kortizol 127 nmol/L. Zbog veličine, brzog rasta i znakova hormonske aktivnosti tumora učinjena je lijevostrana laparoskopska adrenalektomija i limfadenektomija. Patohistološka dijagnoza (PHD) je bila adrenokortikalni onkocitom, bez morfoloških karakteristika koje bi govorile u prilog malignom tumorskom potencijalu prema Bisceglia klasifikaciji. Postoperativna endokrinološka reevaluacija je pokazala urednu vrijednost androgena i slobodnog kortizola u 24 h urinu: androstendion 5,4 nmol/L, DHEAS 11,4 umol/L, kortizol 80 nmol/dU. Daljnje kontrole nisu bile potrebne.

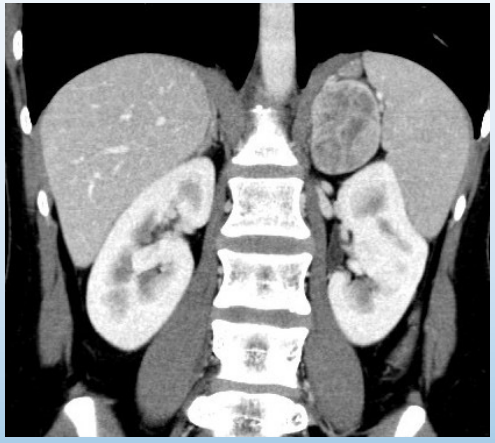
Rasprava: Najčešći incidentalomi nadbubrežnih žlijezda su adenomi, koji imaju tipične morfološke osobine na CT-u i MR-u. Međutim, ako incidentalom nadbubrežne žlijezde na slikovnim tehnikama nema tipične morfološke osobine adenoma, u diferencijalnoj dijagnozi treba razmotriti i ostale rjeđe tumore. Prema smjernicama, incidentalom nadbubrežne žlijezde >4 cm i >10 HU je moguće maligan te mora se razmotriti operativna terapija. Ako je tumor većih dimenzija, smješten u lijevoj nadbubrežnoj žlijezdi te osobito u mladih žena, u diferencijalnoj dijagnozi treba uzeti u obzir adrenokortikalni onkocitom. Adrenokortikalni onkocitomi su najčešće afunkcionalni. Funkcionalni tumori su rijetki i klinički se najčešće prezentiraju kao hiperandrogenizam i Cushingov sindrom. Do sada je u dostupnoj literaturi opisano svega 287 slučajeva adrenokortikalnih onkocitoma. Na

slikovnim tehnikama adrenokortikalni onkocitomi pokazuju nespecifične morfološke karakteristike na nativnim i postkontrastnim slojevima. Dijagnoza se postavlja nakon adrenalektomije, na temelju modificiranih Weiss-ovih PHD kriterija za onkocitne tumore nadbubrežne žlijezde.

Zaključak: Adrenalni onkocitomi i onkocitne neoplazme nesigurnog malignog potencijala su izuzetno rijetki tumori koji imaju izvrsnu prognozu. U literaturi su opisana svega tri slučaja lokalnog recidiva i samo jedan slučaj udaljene metastaze četiri godine nakon adrenalektomije.

Ključne riječi: rijetki tumori, adrenalni incidentalom, adrenalni onkocitom

Literatura: [1] Coppola Bottazzi E, Gambardella C, Mongardini FM, Vanella S, Noviello A, Palma T i sur. Prognosis of Adrenal Oncocytic Neoplasms (AONs): Literature Review of 287 Cases and Presentation of the Oldest Patient. J Clin Med. 2023 Nov 4;12(21):6925.; [2] Ferreira Barros II, Manso F, Teixeira M, Silva Lopes Pereira MR. Case Report of a Rare Adrenocortical Oncocytoma Suspected to be an Adrenal Carcinoma. touchREV Endocrinol. 2021 Apr;17(1):71-74.; [3] Sakano M, Wakabayashi Y, Shirota N, Ohno Y, Suketa A, Nagao T i sur. A case of adrenal oncocytoma: reviewing the literature of radiological finding. BJR Case Rep. 2024 Aug 30;10(5):uaae029.; [4] Skołozdrzy T, Wojciechowski J, Lewandowska-Lula M, Halczak M, Romanowski M. Oncocytoma in adrenal gland. Endokrynol Pol. 2024;75(2):232-233.; [5] Hong Y, Hao Y, Hu J, Xu B, Shan H, Wang X. Adrenocortical oncocytoma: 11 Case reports and review of the literature. Medicine (Baltimore). 2017 Dec;96(48):e8750.



Slika 1. Postkontrastni CT abdomena pokazuje veliki tumor lijeve nadbubrežne žlijezde (strelica).

S10 Adrenocortical oncocytoma — A case report

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Introduction with aim: The aim of this study was to present a rare case of adrenocortical oncocytoma.

Case report: In 2019 a 27-year-old patient was accidentally diagnosed with a left adrenal gland tumor during an abdominal ultrasound examination. Magnetic resonance imaging (MRI) of the abdomen was performed, which described an «adenoma» of the left adrenal gland measuring 25x22 mm. Laboratory tests excluded a hormonally active tumor. It was considered that the tumor was a non-functional adenoma. In 2023 a computerized tomography (CT) of the abdomen revealed a tumor of the left adrenal gland, measuring 55x35 mm, which did not match morphological criteria for an adenoma. In the differential diagnosis, pheochromocytoma was considered. A control MRI of the abdomen confirmed that the tumor did not correspond to an adenoma. The patient was symptom-free, without signs of hypercorticism and hirsutism. The findings of metanephrine and normetanephrine were within the reference intervals, which excluded pheochromocytoma: metanephrine 638 nmol/24 h (RI 0-1300 nmol/24 h), normetanephrine 1014 nmol/24 h (RI 0-2800 nmol/24 h). Laboratory tests were repeated and revealed elevated levels of adrenal androgens and decreased levels of estradiol: DHEAS 23.0 µmol/L, androstenedione 13.2 nmol/L, and estradiol <55 pmol/L. It was impossible to rule out the autonomous secretion of cortisol; in the prolonged suppression test of 48 hours, adequate suppression of cortisol was not achieved: cortisol 127 nmol/L. Due to the tumor's significant size, rapid growth and signs of hormonal activity, laparoscopic left adrenalectomy and lymphadenectomy were performed. The histopathological diagnosis (PhD) was an adrenocortical oncocytoma, without morphological signs that would support malignant tumor potential, according to the Bisceglia classification. Postoperative endocrinological re-evaluation showed normal levels of androgens and free cortisol in 24-hour urine: androstenedione 5.4 nmol/L, DHEAS 11.4 umol/L, cortisol 80 nmol/24 h. No further controls were necessary.

Discussion: The most common incidentalomas of the adrenal glands are adenomas, which have typical morphological features on CT and MRI. However, if an adrenal incidentaloma does not match morphological features typical of an adenoma on imaging studies, other less common tumors should also be considered in the differential diagnosis. According to guidelines, an adrenal incidentaloma of >4 cm and >10 HU is likely malignant and surgery must be considered. If the tumor is large and located in the left adrenal gland, particularly in young women, adrenocortical oncocytoma comes into consideration in the differential diagnosis. Adrenocortical oncocytomas are most

often non-functional. Hormonally active tumors are rare and clinically present as hyperandrogenism and Cushing´s syndrome in most cases. So far, only 287 cases of adrenocortical oncocytomas have been described in the available literature. On imaging studies, adrenocortical oncocytomas show non-specific morphological features on plain and contrast-enhanced scans. The diagnosis is made after adrenalectomy, based on the modified Weiss PhD criteria for oncocytic tumors of the adrenal gland.

Conclusion: Adrenal oncocytomas and oncocytic neoplasms of uncertain malignant potential are exceptionally rare tumors that have an excellent prognosis. Only three cases of local recurrence and only one case of distant metastasis four years after adrenalectomy were described in the literature.

Keywords: rare tumors, adrenal incidentaloma, adrenal oncocytoma

Literature: [1] Coppola Bottazzi E, Gambardella C, Mongardini FM, Vanella S, Noviello A, Palma T i sur. Prognosis of Adrenal Oncocytic Neoplasms (AONs): Literature Review of 287 Cases and Presentation of the Oldest Patient. J Clin Med. 2023 Nov 4;12(21):6925.; [2] Ferreira Barros II, Manso F, Teixeira M, Silva Lopes Pereira MR. Case Report of a Rare Adrenocortical Oncocytoma Suspected to be an Adrenal Carcinoma. touchREV Endocrinol. 2021 Apr;17(1):71-74.; [3] Sakano M, Wakabayashi Y, Shirota N, Ohno Y, Suketa A, Nagao T i sur. A case of adrenal oncocytoma: reviewing the literature of radiological finding. BJR Case Rep. 2024 Aug 30;10(5):uaae029.; [4] Skołozdrzy T, Wojciechowski J, Lewandowska-Lula M, Halczak M, Romanowski M. Oncocytoma in adrenal gland. Endokrynol Pol. 2024;75(2):232-233.; [5] Hong Y, Hao Y, Hu J, Xu B, Shan H, Wang X. Adrenocortical oncocytoma: 11 Case reports and review of the literature. Medicine (Baltimore). 2017 Dec;96(48):e8750.

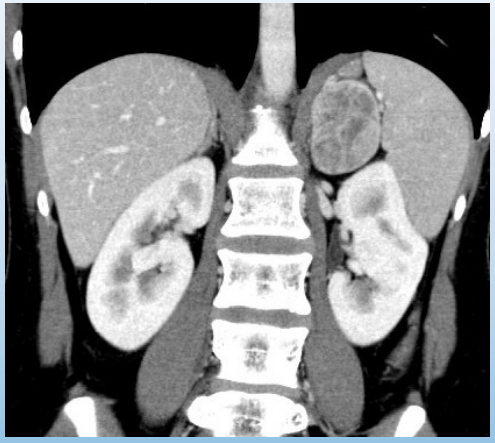

Figure 1. Contrast-enhanced CT of the abdomen shows a large left-sided adrenal mass (arrow).

S11 Feokromocitom: simptomi, dijagnoza i liječenje - prikaz slučaja

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Uvod: Feokromocitom je rijedak neuroendokrini tumor koji nastaje iz kromafinih stanica srži nadbubrežne žlijezde i simpatičkih ganglija te dovodi do hipersekrecije kateholamina, najčešće adrenalina i noradrenalina. Najčešći simptomi su glavobolja, ubrzan rad srca i znojenje, koje karakterizira paroksizmalna pojava. Najčešće su dobroćudni, jednostrani i pojavljuju se između tridesete i pedesete godine života, no u 10-15% slučajeva pojavljuju se u sklopu obiteljskih sindroma, poput multiple endokrine neoplazije tipa 2 (MEN-2). Dijagnoza se postavlja mjerenjem metanefrina i normetanefrina u plazmi i 24-satnom urinu. Metode snimanja kao što su kompjutorizirana tomografija (CT) ili magnetska rezonancija (MRI) koriste se za lokalizaciju tumora. Liječenje je kirurško, a prognoza nakon operacije je odlična.

Prikaz slučaja: Prikazujemo slučaj 41-godišnje bolesnice s anamnezom arterijske hipertenzije u trudnoći i simptomatske hipertenzivne krize. Nakon početne dijagnostičke obrade kod nefrologa, upućena je na dijagnostičku obradu sekundarne hipertenzije kod endokrinologa. Učinjena je MR abdomena kojom je opisana ovalna i oštro ograničena solidna lezija tijela desne nadbubrežne žlijezde dimenzija 25x18x25 mm. Endokrinološkom obradom utvrđene su povišene vrijednosti normetanefrina u plazmi (5x iznad gornje granice normale) i razine normetanefrina u uzorku 24-satnog urina (9x iznad gornje granice normale) što je značilo biokemijsku potvrdu feokromocitoma. Za procjenu pridruženih endokrinih poremećaja unutar MEN-a utvrđene su povišene razine iPTH, bez ultrazvučnih znakova povećanja ili patološki promijenjenih paratireoidnih žlijezda. Scintigrafija je pokazala suspektnu hiperfunkciju gornje lijeve paratireoidne žlijezde. Budući da su vrijednosti kalcija bile normalne, a vrijednosti vitamina D niske, zaključeno je da se vjerojatno radilo o sekundarnom hiperparatireoidizmu. Kontrolirana vrijednost kalcitonina bila je uredna, a UZV štitnjače pokazao je čvorove u oba režnja. Citološkom punkcijom najvećeg čvora pronađeni su nježni koloidi i eritrociti, epitelni elementi nisu nađeni. Nalazi ostalih hormona hipofize i ciljnih žlijezda bili su uredni. Bolesnici je učinjena desnostrana adrenalektomija, a patohistološka analiza potvrdila je dijagnozu feokromocitoma. Tumor je imunohistokemijski bio pozitivan na kromogranin i žarišno na S-100. Povećana ekspresija p53 nije nađena, Ki-67 bio je do 3%, ukupni PASS rezultat 4/20.

Zaključak: Feokromocitom je rijedak tumor koji nema specifične simptome i često ostaje neprepoznat. Ovim prikazom slučaja željeli smo naglasiti važnost otkrivanja feokromocitoma i njegovog liječenja u cilju prevencije visokog kardiovaskularnog morbiditeta i mortaliteta bolesnika. Osim toga, prepoznavanje feokromocitoma u obiteljskim sindromima važno je kako bi se i u ostalih članova obitelji bolesnika pravovremeno moglo započeti liječenje.

S11 Pheochromocytoma: symptoms, diagnosis and treatment — a case report

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Introduction: Pheochromocytoma is a rare neuroendocrine tumor that arises from chromaffin cells of the medulla of the adrenal gland and sympathetic ganglia and leads to hypersecretion of catecholamines, most often adrenaline and noradrenaline. The most common symptoms are headache, palpitations and sweating, which is characterized by paroxysmal occurrence. They are most often benign, unilateral and appear between the ages of thirty and fifty, but in 10-15% of cases they appear as part of family syndromes, such as multiple endocrine neoplasia type 2 (MEN-2). The diagnosis is made by measuring metanephrine and normetanephrine in plasma and in 24-hour urine. Imaging methods such as computed tomography (CT) or magnetic resonance imaging (MRI) are used to localize tumors. Treatment is surgical, and the prognosis after surgery is excellent.

Case report: We present the case of a 41- year- old female patient with a history of arterial hypertension in pregnancy and symptomatic hypertensive crisis. After the initial diagnostic treatment by a nephrologist, she was referred for diagnostic treatment of secondary hypertension by an endocrinologist. Abdominal MRI was performed, which described an oval and sharply limited solid lesion of the body of the right adrenal gland measuring 25x18x25 mm. Endocrinological examination revealed elevated values of normetanephrine in the plasma (5x above the upper limit of normal) and levels of normetanephrine in the 24-hour urine sample (9x above the upper limit of normal) which would mean biochemical confirmation of pheochromocytoma. In order to evaluate associated endocrine disorders within MEN, elevated levels of iPTH were found, without ultrasound signs of enlarged or pathologically changed parathyroid glands. Scintigraphy showed suspicious hyperfunction of the upper left parathyroid gland. Since the calcium values were normal and the vitamin D values were low, it was concluded that this was probably secondary hyperparathyroidism. The controlled value of calcitonin was normal, and ultrasound of the thyroid showed nodules in both lobes. Cytological puncture of the largest node revealed some delicate colloid and erythrocytes, epithelial elements were not found. Findings of other pituitary hormones and target glands were normal. The patient underwent a right-sided adrenalectomy, and the received pathohistological diagnosis was pheochromocytoma, immunohistochemically positive for chromogranin and focally for S-100. Increased expression of p 53 was not found, Ki-67 was up to 3%, total PASS score 4/20.

Conclusion: Pheochromocytoma is a rare tumor that does not have specific symptoms and often remains unrecognized. In this case report, we wanted to emphasize the importance of detecting pheochromocytoma and its treatment in order to prevent high cardiovascular morbidity and mortality in patients. In addition, recognition of pheochromocytoma in family syndromes is important so that other members of the patient´s family can be treated in time.

S12 Prikaz bolesnice s netipičnom kliničkom prezentacijom feokromocitoma

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Uvod s ciljem: Prikazat ćemo 55-godišnju bolesnicu koja je hospitalizirana putem hitne službe na Odjel zbog tromboze donje šuplje vene. Cilj ovog sažetka upozoriti da unatoč urednim vrijednostima arterijskog tlaka kod bolesnice je dijagnostičkom obradom uzroka tromboze dijagnosticiran feokromocitom.

Prikaz slučaja: Radi se o 55-godišnja bolesnica s višegodišnjom astmom koja je 2016. g. obrađivana i liječena pod sumnjom na ehinokoknu cistu jetre u Klinici za infektivne bolesti, iako punkcijom tvorbe nisu bili dokazani paraziti u tvorbi. U 7. mj. 2024. započeta je gastroenterološka obrada zbog ponovnih bolova u abdomenu. Tijekom hospitalizacije učinjen je CT-abdomena i zdjelice kojim je nađena tvorba desne nadbubrežne žlijezde otvorene etiologije uz trombozu donje šuplje vene.

Rasprava: Učinjena je endokrinološka obrada kojom je testom supresije s 1 mg deksametazona zabilježena zadovoljavajuća supresija kortizola. U 24-satnom urin zabilježene su povišene razine norepinefrina, čime je biokemijski verificiran feokromocitom. Čitavo vrijeme hospitalizacije bolesnica je imala uredne vrijednosti krvnog tlaka zbog čega smo se odlučili za minimalna dozu alfa-blokatora, a potom je s oprezom uvedena i minimalna doza beta-blokatora. Nakon adekvatne pripreme kod bolesnice je uspješno i bez komplikacija laparoskopski odstranjena desna nadbubrežna žlijezda a patohistološki je verificiran feokromocitom s potencijalno biološki agresivnim ponašanjem.

Zaključak: Ovaj slučaj naglašava važnost sveobuhvatnog pristupa u dijagnostici i liječenju bolesnika s nespecifičnim i netipičnim kliničkim slikama, kao i potrebu za daljnjim istraživanjem endokrinoloških aspekata u kontekstu radiološki opisanih tvorbi nadbubrežne žlijezde.

Ključne riječi: tromboza donje šuplje vene, feokromocitom, nadbubrežna žlijezda

S12 Presentation of a patient with an atypical clinical presentation of pheochromocytoma

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Introduction and Objective: We present the case of a 55-year-old female patient who was admitted to the hospital through the emergency department due to thrombosis of the inferior vena cava. fan m of this summary is to highlight that, despite normal blood pressure values, further diagnostic evaluation of the thrombosis led to the diagnosis of pheochromocytoma.

Case Presentation: This is a 55-year-old female patient with a long-standing history of asthma. In 2016, she was evaluated and treated at the Clinic for Infectious Diseases under suspicion of a hepatic echinococcal cyst; however, aspiration of the lesion did not confirm the presence of parasites. In July 2024, a gastroenterological workup was initiated due to recurrent abdominal pain. During hospitalization, a CT scan of the abdomen and pelvis revealed a mass in the right adrenal gland of uncertain etiology, along with thrombosis of the inferior vena cava.

Discussion: Endocrinological evaluation was performed, and suppression testing with 1 mg dexamethasone demonstrated adequate cortisol suppression. A 24-hour urine analysis revealed elevated norepinephrine levels, confirming the biochemical diagnosis of pheochromocytoma. Throughout hospitalization, the patient maintained normal blood pressure values, prompting the decision to initiate only a minimal dose fan alpha-blocker, followed cautiously by a low-dose beta-blocker. After adequate preoperative preparation, the patient successfully underwent laparoscopic adrenalectomy of the right adrenal gland without complications. Histopathological examination confirmed pheochromocytoma with potentially aggressive biological behavior.

Conclusion: This case underscores the importance of a comprehensive approach in diagnosing and treating patients with nonspecific and atypical clinical presentations. It also highlights the need for further investigation into the endocrine aspects of radiologically detected adrenal gland lesions.

Key words: thrombosis of the inferior vena cava, pheochromocytoma, adrenal gland

S13 Cushingova bolest / sindrom i trudnoća – prikaz slučaja

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Uvod: Pacijentice s Cushingovom bolesti/sindromom rijetko ostvaruju trudnoću, obzirom da su zbog ekscesa kortizola često amenoroične ili imaju anovulatorne cikluse. Za razliku od pacijentica koje nisu trudne i kod kojih je značajno učestaliji ACTH-ovisan hiperkortizolizam (Cushingova bolest), kod trudnica je češći ACTH-neovisan hiperkortizolizam (Cushingov sindrom), u najvećem broju slučaja adrenalni adenom. Kod većine slučajeva Cushingovog sindroma ili Cushingove bolesti u trudnoći radi se o novodijagnosticiranim bolestima.

Prikaz slučaja: U ovom prikazu slučaja riječ je od 27-godišnjoj pacijentici kod koje je godinu dana iza poroda otkriven Cushingov sindrom. Sam tijek trudnoće bio je uredan do 6. mjeseca trudnoće kada je od strane medicinske sestre iz ginekološke ambulante primjećeno da je pacijentica neuobičajeno otečena u licu, uz pojavu strija ne samo na trbuhu, već i po koži nadlaktica i natkoljenica. Nije bilo drugih kliničkih značajki koje bi upućivale na hiperkotizolizam. Godinu dana iza poroda pojava noćnog znojenja, porast na tjelesnoj masi, otečenost lica. Dijagnostikom je otkriven adenom desne nadbubrežne žlijezde koji je operativno odstranjen. Obzirom na simptome koji su se pojavili tijekom trudoće, pretpostavljamo da se prije trudnoće radilo o subkliničkom Cushingu, koji se vjerojatno pod utjecajem promijenjenog hormonskog miljea u trudnoći aktivirao.

Zaključak: Dijagnoza Cushingove bolesti/sindroma je izazovna u trudnoći, radi preklapajućih kliničkih slika i simptoma hiperkortizolizma i fizioloških promjena u trudnoći te preklapajućih komplikacija kao što su arterijska hipertenzija, hiperglikemija, izrazitije povećanje tjelesne mase. Ukoliko su simptomi izraženiji, npr. pojava arterijske hipertenzije rano u trudnoći, izrazita hiperglikemija, prekomjerni porast na tjelesnoj masi, otečenost lica, izraženije strije, učiniti slobodni kortizol u 24h urinu, osnosno kortizol iz sline u ponoć, što nam može ukazati na dijagnozu. Što ranije liječenje nužno je radi mogućih teških posljedica i za majku i za dijete.

Ključne riječi: Cushingov sindrom, leukocitoza, adenom nadbubrežne žlijezde

Literatura: [1] Lynnette K Nieman. Diagnosis and management of Cushing syndrome during pregnancy (web pages), UptoDate, last updated: Dec 18, 2023., Literature review current through: Dec 2024. https://www.uptodate.com/contents/search; [2] Frédéric Castinetti, Thierry Brue. Impact of Cushing´s syndrome on fertility and pregnancy. 2022 Jun;83(3):188-190.doi:10.1016/j.ando.2022.04.001. Epub 2022 Apr 17.; [3] Nada Younes , Matthieu St-Jean, Isabelle Bourdeau, André Lacroix. Endogenous Cushing´s syndrome during pregnancy. 2023 Feb;24(1):23-38. doi: 10.1007/s11154-022-09731-y. Epub 2022 Jun 7.

S13 Cushing's disease/syndrome and pregnancy – a case report

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Introduction and Aim: Patients with Cushing´s disease/syndrome rarely become pregnant since they are frequently amenorrheic or have anovulatory cycles as a result of high cortisol (1,2). ACTH-dependent hypercortisolism (Cushing's disease) is far more common in women who are not pregnant. In pregnant women, however, ACTH-independent hypercortisolism (Cushing´s syndrome) is far more common. The majority of occurrences of Cushing´s syndrome or Cushing´s disease during pregnancy are new diagnoses caused by adrenal adenoma(1). We shall introduce a patient who discovered Cushing´s syndrome a year after giving birth.

Case presentation: This case report concerns a 27-year-old woman who was diagnosed with Cushing´s syndrome one year after delivering birth. The pregnancy progressed normally until the sixth month, when the nurse from the gynecological clinic noticed that the patient´s face was unusually swollen, with stretch marks forming not only on the stomach but also on the skin of the upper arms and legs. There were no other clinical indicators of hypercortisolism. A year after giving birth, the patient developed night sweats, weight increase, and facial swelling. An adenoma of the right adrenal gland was discovered during the diagnostic process and surgically removed.

Discussion: Based on the symptoms that developed during pregnancy, we assume that it was preclinical Cushing's before pregnancy, which was likely activated by the altered hormonal milieu during pregnancy.

Conclusion: Diagnosing Cushing's disease or syndrome during pregnancy might be difficult due to the similarities between the signs and symptoms of hypercortisolism and the physiological changes that occur throughout pregnancy(1). Complications such as high blood pressure, high blood sugar, and substantial weight gain might occur simultaneously(3). Some of the most evident indicators of pregnancy include high blood pressure in the arteries early on, high blood sugar, weight gain, face swelling, and more visible stretch marks(3). Free cortisol levels in urine collected during the day, as well as salivary cortisol levels at midnight, can help confirm the diagnosis(1). Early intervention is required due to the potentially devastating effects for both the mother and the child.

Key words: hypercortisolism, Cushing´´s disease/syndrome, pregnancy

Literature: [1] Lynnette K Nieman. Diagnosis and management of Cushing syndrome during pregnancy (web pages), UptoDate, last updated: Dec 18, 2023., Literature review current through: Dec 2024. https://www.uptodate.com/contents/search
[2] Frédéric Castinetti, Thierry Brue. Impact of Cushing´s syndrome on fertility and pregnancy. 2022 Jun;83(3):188-190.doi:10.1016/j.ando.2022.04.001. Epub 2022 Apr 17.; [3] Nada Younes , Matthieu St-Jean, Isabelle Bourdeau, André Lacroix. Endogenous Cushing´s syndrome during pregnancy. 2023 Feb;24(1):23-38. doi: 10.1007/s11154-022-09731-y. Epub 2022 Jun 7.

S14 Leukocitoza kao prva manifestacija Cushingovog sindroma

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Uvod s ciljem: Cushingov sindrom karakterizira prekomjerna razina kortizola u krvi koja dovodi do niza metaboličkih poremećaja s posljedičnim razvojem visceralne pretilosti, arterijske hipertenzije, poremećaja metabolizma glukoze, dislipidemije te mnogih drugih komplikacija.Cilj ovog prikaza slučaja naglasiti je leukocitozu kao jednu od manifestacija, posebice u ranim stadijima bolesti.

Prikaz slučaja: 42-godišnja bolesnica bez značajnih komorbiditeta pratila se unazad 5 godina zbog leukocitoze s neutrofilijom. Prethodno je učinjena hematološka obrada kojom nije nađeno uzroka. Upućena je endokrinologu zbog značajnog porasta na tjelesnoj masi unazad godinu dana, posebice u području trbuha. Unazad nekoliko mjeseci zbog povišenih vrijednosti krvnog tlaka uvedena joj je antihipertenzivna terapija. Obradom putem Dnevne bolnice učinjen je ultrazvuk abdomena, a potom MSCT kojim je opisan adenom desne nadbubrežne žlijezde. Iz laboratorijskih nalaza izdvajaju se povišene vrijednosti kortizola uz suprimiran ACTH, osatli nalazi hormona adenohipofize su bili uredni. Prekonoćnom blokadom jednim miligramom deksametazona nije postignuta supresija lučenja kortizola, a sve navedeno govori u prilog Cushingovom sindromu uslijed hormonske aktivnosti opisanog adenoma desne nadbubrežne žlijezde. Vrijednosti HOMA-IR-a ukazale su na postojanje inzulinske rezistencije te je dodatno zabilježena i hiperkolesterolemija. Po postavljanju dijagnoze indiciran je operativni zahvat te je učinjena desnostrana adrenalektomija, a bolesnici je uvedena nadomjesna terapija hidrokortizonom.

Rasprava: Leukocitoza uz neutrofiliju karakterističan je nalaz u Cushingovom sindromu(1,2). Kortizol ima direktan i indirektan učinak na bijele krvne stanice. Potiče otpuštanje polimorfonukleara u cirkulaciju, odgađa apoptozu neutrofila, smanjuje ulazak stanica u tkiva te potiče otpuštanje marginaliziranih neutrofila i produljuje njihov intravaskularni životni vijek (3). Kod bolesnice se leukocitoza bez jasnog uzroka pratila unazad nekoliko godina, a tek je po razvoju klinički vidljivih manifestacija upućena na pregled endokrinologa. Cushingov sindrom rijedak je poremećaj te ga je u ranim fazama teško razlikovati od metaboličkog sindroma, posebice u kontekstu današnjeg trenda porasta pretilosti. Dijagnoza se najčešće postavlja tek po razvoju klasične kliničke slike uz već razvijene komplikacije.

Zaključak: Rana sumnja i postavljanje dijagnoze Cushingovog sindroma otežani su zbog velike prevalencije sličnih simptoma u bolesnika bez hiperkortizolemije.Ovaj prikaz slučaja pokazuje kako bi leukocitoza mogla biti rani indikator Cushingovog sindroma te naglašava važnost isključivanja endokrinoloških uzroka leukocitoze.

Ključne riječi: Cushingov sindrom, leukocitoza, adenom nadbubrežne žlijezde

Literatura: [1] Masri-Iraqi H, Rudman Y, Shochat T, Kushnir S, Shimon I, Fleseriu M, Akirov A. Leukocytosis in Cushing´s syndrome persists post-surgical remission and could predict a lower remission prognosis in patients with Cushing´s disease. J Endocrinol Invest. 2025 Jan 28. doi: 10.1007/s40618-025-02535-2. Epub ahead of print. PMID: 39873891.; [2] Paja M, Merlo I, Rodríguez-Soto J, Cruz-Iglesias E, Moure MD, Elías C, Oleaga A, Egaña N. White blood cell count: a valuable tool for suspecting Cushing´s syndrome. J Endocrinol Invest. 2023 Jan;46(1):141-149. doi: 10.1007/s40618-022-01892-6. Epub 2022 Aug 9. PMID: 35943722.; [3] Masri-Iraqi H, Robenshtok E, Tzvetov G, Manistersky Y, Shimon I. Elevated white blood cell counts in Cushing´s disease: association with hypercortisolism. Pituitary. 2014 Oct;17(5):436-40. doi: 10.1007/s11102-013-0522-0. PMID: 24078318.

S14 Leukocytosis as the first manifestation of Cushing's syndrome

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Introduction with the aim: Cushing´s syndrome is characterized by an excessive level of cortisol in the blood, which leads to a series of metabolic disorders with the consequent development of visceral obesity, arterial hypertension, glucose metabolism disorders, dyslipidemia and many other complications. This case report emphasizes leukocytosis as one of the manifestations, especially in the early stages of the disease.

Case report: A 42-year-old patient without notable comorbidities was monitored for 5 years due to leukocytosis characterized by neutrophilia.Hematological evaluations were previously conducted, but the underlying etiology remained unidentified. She was referred to an endocrinologist due to a substantial escalation in body mass over the preceding year, particularly concentrated in the abdominal region. Several months prior, antihypertensive medication was initiated due to the patient's elevated blood pressure measurements. An ultrasound of the abdomen was performed, followed by an MSCT, which revealed an adenoma of the right adrenal gland. The laboratory findings revealed elevated cortisol levels coupled with suppressed adrenocorticotropic hormone levels, while the function of the anterior pituitary gland remained within normal limits.Overnight administration of one milligram of dexamethasone failed to suppress cortisol production, which is consistent with Cushing´s syndrome secondary to the hormonal activity of the identified adenoma in the right adrenal gland. Results additionally revealed the presence of insulin resistance, as indicated by elevated HOMA-IR values, and the existence of hypercholesterolemia. Additionally, thyroid function tests demonstrated normal levels of TSH, T3, and T4, while the assessment of antibody titers ruled out the presence of autoimmune thyroid disease.Following the diagnosis, a right-sided adrenalectomy was performed, and the patient received replacement therapy with hydrocortisone.

Discussion: Leukocytosis with neutrophilia is a characteristical finding in Cushing´s syndrome (1,2). Cortisol has a direct and indirect effect on white blood cells. It promotes the release of polymorphonuclear cells into circulation, delays the apoptosis of neutrophils, reduces the entry of cells into tissues, promotes the release of marginalized neutrophils, and prolongs their intravascular life span (3). The patient's unexplained leukocytosis has been monitored for several years, and only after the development of clinically visible manifestations was she referred to an endocrinologist for examination. Cushing´s syndrome is a rare disorder, and in the early stages, it is difficult to distinguish it from metabolic syndrome, especially in the context of today's trend of increasing

obesity. The diagnosis is usually established only after the development of the classic clinical picture with already-developed complications.

Conclusion: Early suspicion and diagnosis of Cushing´s syndrome are difficult due to the high prevalence of similar symptoms in patients without hypercortisolemia. This case report shows that leukocytosis could be an early indicator of Cushing's syndrome and emphasizes the importance of ruling out endocrinological causes of leukocytosis.

Keywords: Cushing's syndrome, leukocytosis, adenoma of the adrenal gland

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S15 Dijagnostički algoritam obrade primarnog aldosteronizma

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Uvod: Primarni aldosteronizam je najčešći uzrok sekundarne hipertenzije s prevalencijom od 6% među hipertoničarima u primarnoj zdravstvenoj zaštiti. Autonomno lučenje aldosterona iz jedne ili iz obje nadbubrežne žlijezde dovodi do značajno većeg kardiovaskularnog rizika i bubrežnog oštećenja nego kod esencijalne hipertenzije.

Prikaz slučaja: U prikazu slučaja je opisan pacijent kod kojeg je zbog hipokalijemije i rezistentne hipertenzije postavljena sumnja na primarni aldosteronizam. Učinjena je obrada, isključeni su drugi endokrinološki uzroci hipertenzije. Uz standardnu laboratorijsku obradu, test supresije 0,9% fiziološkom otopinom, slikovnu obradu, učinjena je i kateterizacija nadbubrežnih vena kako bi razlikovali unilateralnu od bilateralne bolesti jer ponekad sam nalaz CT-a nije dovoljan. Dokazana je unilateralna bolest nadbubrega te je potom učinjena laparoskopska adrenalektomija.

Rasprava: Kod pacijenta s rezistentnom hipertenzijom, diferencijalno dijagnostički treba pomisliti o mogućem sekundarnom uzroku hipertenzije. Nakon što smo isključili druge endokrinološke uzroke sekundarne hipertenzije poput bolesti štitnjače i hiperkortizolizma, postavljena je sumnja na primarni aldosteronizam koji je jedan od najčešćih uzroka sekundarne hipertenzije Laboratorijskom i slikovnom obradom je potvrđena dijagnoza, a kateterizacijom nadbubrežnih vena smo i dokazali unilateralnu bolest nadbubrega.

Zaključak: Kod dokazane unilateralne bolesti laparoskopska adrenalektomija u većine pacijenata dovodi do normalizacije ili sniženja krvnog taka, kao i korekcije hipokalijemije. Drugim riječima, uzrok sekundarne hipertenzije je moguće izliječiti za razliku od primarne hipertenzije.

Ključne riječi: rezistentna hipertenzija, primarni aldosteronizam, kateterizacija nadbubrežnih vena.

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S15 Diagnostic Algorithm in Primary Aldosteronism

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Introduction: Primary aldosteronism is the most common form of secondary hypertension, with a prevalence of 6% among hypertensive patients in primary care practice. Autonomous and secretion of aldosterone from one or both adrenal glands in patients with primary aldosteronism causes significantly higher cardiovascular risk and more renal damage compared to equally severe essential hypertension

Case report: In this case report our patient had hypokalemia and resistant hypertension, we suspected primary aldosteronism. After excluding other secondary causes of hypertension, laboratory tests and CT imaging, we considered adrenal vein sampling to distinguish between unilateral or bilateral aldosteron production, because relying on CT imaging is not enough. We proved it was a unilateral disease, after which the patient undergone laparoscopic adrenalectomy.

Discussion: In a patient with resistant hypertension, in differential diagnosis, we should think about secondary causes of hypertension. After excluding other possible causes of secondary hypertension like thyroid diseases or hypercortisolism, we suspected primary aldosteronism which is one of the most common causes of secondary hypertension. After confirming the diagnosis with laboratory testing, adrenal vein sampling proved unilateral disease.

Conclusion: In most patients with diagnosed unilateral disease of the adrenal glands, laparascopic adrenalectomy is an therapeutic option for regulating or normalizing hypertension and potassium. In other words sometimes we can treat causes of secondary hypertension, unlike primary hypertension.

Key words: resistant hypertension, primary aldosteronism, adrenal vein sampling

Literature: [1] Literatura:1.Mulatero P, Monticone S, Deinum J, Amar L, Prejbisz A, Zennaro MC, Beuschlein F, Rossi GP, Nishikawa T, Morganti A, Seccia TM, Lin YH, Fallo F, Widimsky J.Genetics, prevalence, screening and confirmation of primary aldosteronism: a position statement and consensus of the Working Group on Endocrine Hypertension of The European Society of Hypertension. J Hypertens. 2020 Oct;38(10):1919-1928. doi: 10.1097/HJH.0000000000002510.; [2] Carey RM, Wright JT Jr, Taler SJ, Whelton PK. Share Guideline-Driven Management of Hypertension: An Evidence-Based Update. Circ Res. 2021 Apr 2;128(7):827-846. doi: 10.1161/CIRCRESAHA.121.318083. Epub 2021 Apr 1.3 John Watson Funder Primary Aldosteronism: Where Are We Now? Where to from Here? Horm Metab Res. 2020 Jun;52(6):459-466. doi: 10.1055/a-1120-8623.

OSTEOPOROZA I METABOLIZAM KALCIJA

S16 Hipoparatireoidizam kao uzrok ponavljanih ventrikulskih tahikardija

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Prikaz slučaja: Radi se o 68-godišnjoj pacijentici s dugogodišnjim pušačkim statusom u anamnezi (25 pack/years) koja se hospitalizira u Koronarnu jedinicu Klinike za bolesti srca i krvnih žila Kliničkog bolničkog centra u Splitu zbog bolova u prsima uz elektrokardiografske promjene po tipu akutnog infarkta miokarda s elevacijom ST spojnice te produljen QT interval (460 ms). Žurnom invazivnom koronarografijom utvrdi se okluzija srednjeg segmenta prednje silazne grane lijeve koronarne arterije te se uradi uspješna perkutana koronarna intervencija s postavljanjem potpornice koja otpušta lijek. Zbog bolova u prsima sljedećeg dana uradi se rekoronarografija kojom se verificira uredan protok u segmentu prethodno postavlje potpornice. U daljnjem tijeku hospitalizacije pacijentica postaje hemodinamski nestabilna, dispnoična, cijanotična, te se endotrahealno intubira i mehanički ventilira. Ehokardiografski se verificira ishemijska kardiomiopatija teško narušene sistoličke funkcije uz ožiljak i recentni ispad kontraktiliteta lijeve klijetke. Po stabilizaciji kliničkog stanja, pacijenticu se odvoji od mehaničke ventilacije te ekstubira. U daljnjem kliničkom tijeku pacijentica je respiracijski stabilna, ali se ritmološki bilježe učestale ventrikulske tahikardije zbog kojih je u više navrata i defibrilirana. U laboratorijskim nalazima bilježi se porast upalnih parametara u sklopu prateće uroinfekcije (leukociti 16.4x109/L, C-reaktivni protein 332.5 umol/L), narušena bubrežna funkcija (ureja 17.0 mmol/L, kreatinin 138 umol/L, eGFR 33.9 mL/min/1.73m2), uredne vrijednosti natrija (135 mmol/L), kalija (4,5 mmol/L) i magnezija (0,80 mmol/L), snižene vrijednosti vitamina D (<7.5 nmol/L), ukupnog kalcija (0,73 mmol/L) i ioniziranog kalcija (0.63 mmol/L), povišene vrijednosti fosfora (3,09 mmol/L) i nemjerljive vrijednosti paratireoidnog hormona (<0,6 mmol/L) te se nakon konzilijarnog pregleda endokrinologa postavi dijagnoza hipoparatiroidizma. Nakon provedene intenzivirane nadomjesne terapije klacijevim glukonatom, kalcijevim karbonatom, kalcitriolom, kolekalciferolom, te pripravcima magnezija, dolazi do normalizacije vrijednosti elektrolita u serumu uz kliničku stabilizaciju te se pacijentica otpušta iz Koronarne jedinice u klinički stabilnom stanju, eupnoična, normotenzivna, normofrekventnog sinus ritma.

Rasprava: Hipoparatireoidizam je rijetko stanje karakterizirano manjkom paratireoidnog hormona koje u više od 75% slučajeva nastaje nakon uklanjanja ili oštećenja jedne ili više doštitnih žlijezda prilikom kirurških zahvata na štitnoj žlijezdi. Ukoliko se pak radi o genetskoj formi (manje od 10% ukupnog broja slučajeva) hipoparatireoidizma (npr. u sklopu DiGeorge sindroma ili autoimunog poliendokrinog sindroma tip 1), u kojem paratireodine žlijezde nedostaju ili su atrofične, takvo stanje se obično javlja

se u djetinjstvu. Ostali rijetki uzroci koji mogu dovesti do hipoparatireoidizma su hemokromatoza, Wilsonova bolest, radioterapija te metastaze određenih maligniteta. Hipoparatireoidizam se može pojaviti i bez jasne etiologije, kada je vjerojatno da se radi o autoimunom obliku bolesti (1), što je vjerojatno slučaj i kod prikazane pacijentice. Od ranije je uočena povezanost hipokalcemije s ventrikularnim aritmijama, posebice aritmija po tipu „torsade de pointes“, uslijed produljenja QT intervala. U literaturi je opisano nekoliko slučajeva monomorfne ventrikulske tahikardije zbog hipokalcijemije. Cecchi i suradnici opisali su pacijenticu sa simptomatskim ventrikulskim tahikardijama koje se pripisuju hipokalcijemiji, budući su aritmije prestale suplementacijom kalcija, međutim, u tom slučaju poremećaj elektrolita bio je posljedica od ranije poznatog kroničnog bubrežnog zatajenja (2).

Zaključak: Iako je moguće da se u ovom slučaju radilo i o reperfuzijskim ventrikulskim tahikardijama nakon akutnog infarkta miokarda, budući je došlo do stabilizacije srčanog ritma tek po korekciji elektrolitskog statusa, vjerojatno je da je kod naše pacijentice upravo teška hipokalcemija u sklopu hipoparatireoidizma bila provocirajući čimbenik ponavljanih ventrikulskih tahikardija.

Literatura: [1] **Bilezikian JP. Hypoparathyroidism. J Clin Endocrinol Metab. 2020. 105:1722-36.;** [2] **Cecchi E, Grossi F, Rossi M, Giglioli C, De Feo ML. Severe hypocalcemia and life-threatening ventricular arrhytmias: case report and proposal of a diagnostic and therapeutic algorithm. Clin Cases Miner Bone Metab. 2015. 12:265-8.**

S16 Hypoparathyroidism as a cause of recurrent ventricular tachycardias

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Case report: 68-year-old female patient with a long history of smoking (25 pack/years) who was hospitalized in the Coronary Unit of the Clinic for Heart and Blood Vessel Diseases due to chest pain, along with electrocardiographic changes suggestive of acute myocardial infarction with ST-segment elevation and prolonged QT interval (460 ms). Invasive coronary angiography revealed an occlusion of the middle segment of the anterior descending branch of the left coronary artery, followed by a successful percutaneous coronary intervention with the placement of a drug-eluting stent.
Due to ongoing chest pain the following day, a repeat coronary angiography was performed, confirming normal blood flow in the segment where the stent was previously placed. During the further hospitalization, the patient became hemodynamically unstable, dyspnoeic, and cyanotic, and was intubated and mechanically ventilated. Echocardiography confirmed ischemic cardiomyopathy with severely impaired systolic function, a scar, and recent loss of contractility in the left ventricle. After clinical stabilization, the patient was weaned off mechanical ventilation and extubated. In the following days the patient remained respiratory stable but experienced frequent ventricular tachycardias, for which she was defibrillated multiple times. Laboratory findings showed an increase in inflammatory markers due to a concurrent urinary tract infection (leukocytes 16.4x10^9/L, C-reactive protein 332.5 mg/L), impaired kidney function (urea 17.0 mmol/L, creatinine 138 µmol/L, eGFR 33.9 mL/min/1.73m2), normal sodium (135 mmol/L), potassium (4.5 mmol/L), and magnesium (0.80 mmol/L) levels, decreased vitamin D (<7.5 nmol/L), total calcium (0.73 mmol/L), and ionized calcium (0.63 mmol/L) levels, elevated phosphorus (3.09 mmol/L), and undetectable parathyroid hormone (<0.6 mmol/L) levels. After a consultation with an endocrinologist, a diagnosis of hypoparathyroidism was made. Following intensive replacement therapy with calcium gluconate, calcium carbonate, calcitriol, cholecalciferol, and magnesium supplements, the electrolyte levels normalized, and the patient clinically stabilized with no more cardiac arrhythmias recorded in electrocardiogram. She was discharged from the Coronary Unit in a clinically stable condition, eupnoeic, normotensive, and in normal sinus rhythm.

Discussion: Hypoparathyroidism is a rare condition characterized by a deficiency of parathyroid hormone, which in more than 75% of cases occurs after the surgical removal or damage of one or more parathyroid glands during surgical procedures on the thyroid gland. If it is a genetic form of hypoparathyroidism (less than 10% of all cases) (e.g., as part of DiGeorge syndrome or autoimmune polyendocrine syndrome type 1), in which the parathyroid glands are either absent or atrophic, this condition typically appears in

childhood. Other rare causes of hypoparathyroidism include hemochromatosis, Wilson´s disease, radiotherapy, and metastases from certain malignancies. Hypoparathyroidism may also occur without a clear etiology, in which case it is likely an autoimmune form of the disease (1), which is probably the case with the presented patient. There has been a previously observed and explained association between hypocalcemia and ventricular arrhythmias, particularly arrhythmias of the ‹torsades de pointes' type, due to prolonged QT interval. Several cases of monomorphic ventricular tachycardia caused by hypocalcemia have been described in the literature. Cecchi et al. described a patient with symptomatic ventricular tachycardias attributed to hypocalcemia, as the arrhythmias resolved with calcium supplementation. However, in that case, the electrolyte disturbance was a consequence of previously known chronic renal failure (2).

Conclusion: Although it is possible that the patient in this case also experienced reperfusion-related ventricular tachycardias following acute myocardial infarction, as stabilization of the heart rhythm occurred only after electrolyte status correction, it is more likely that severe hypocalcemia in the context of hypoparathyroidism was the triggering factor for the recurrent ventricular tachycardias in our patient.

Literature: ¹ Bilezikian JP. Hypoparathyroidism. J Clin Endocrinol Metab. 2020. 105:1722-36.; ² Cecchi E, Grossi F, Rossi M, Giglioli C, De Feo ML. Severe hypocalcemia and life-threatening ventricular arrhytmias: case report and proposal of a diagnostic and therapeutic algorithm. Clin Cases Miner Bone Metab. 2015. 12:265-8.

S17 Klinički izazovi u dijagnozi, liječenju i praćenju postpartalne osteoporoze

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Uvod: Osteoporoza je kronična progresivna metabolička bolest koštanog sustava obilježena smanjenjem mineralne gustoće, a prema etiologiji dijeli se na primarnu i sekundarnu osteoporozu. Postpartalna osteoporoza, odnosno osteoporoza povezana s trudnoćom i dojenjem (eng. pregnancy and lactation-associated osteoporosis, PLO) oblik je sekundarne osteoporoze definirane pojavom netraumatskih prijeloma tijekom trećeg tromjesečja trudnoće i/ili prvih mjeseci nakon poroda, a najčešće je riječ o kompresivnim vertebralnim prijelomima. PLO je iznimno rijetka, s indicidencijom oko 0,4 na 10000 žena (1, 2).

Prikaz slučaja: Ovaj prikaz slučaja prikazuje bolesnicu, sada u dobi od 45. godina, kojoj je u 36. godini nakon drugog poroda dijagnosticirana pospartalna osteoporoza. Riječ je o bolesnici koja je do sada imala dva poroda, prvi puta 2008. hitnim carskim rezom u 38. tjednu trudnoće, te drugi puta 2016. godine kada je rodila blizance. Bolesnica je prethodno trudnoći imala četiri spontana pobačaja, zbog čega je učinjena dodatna obrada po transfuziologu te je utvrđena mutacija faktora V Leiden, te je po preporuci transfuziologa tijekom obje trudnoće primala niskomolekularni heparin od 5. tjedna trudnoće. Već nakon prvog carskog reza bolesnica je imala bolove u kralježnici, koji su se povukli uz redovito vježbanje. Nakon drugog poroda, bolovi su se intenzivirali te je učinjen RTG torakalne i lumbosakralne kralježnice kojim su opisani anteklinasto oblikovani trupovi Th10 i Th11 te bikonkavno oblikovani trupovi Th6, L1, L2, L3 i L4, odnosno kompresivne frakture trupova kralježaka posljedično osteoporozi. Bolesnica je pregledana po ortopedu, te je kroz određeno razdoblje bila opskrbljena ortozom, a provela je i fizikalnu rehabilitaciju. Učinjen je pregled kliničkog farmakologa, koji je zaključio da opisana osteoporoza u bolesnice moguće i posljedica dugoročne primjene niskomolekularnog heparina. U terapiju je uključen teriparatid, kojeg je bolesnica primala kroz dvije godine, do studenog 2020. godine, nakon toga je nastavljena samo supstitucija vitamina D. Na posljednjoj kontroli u siječnju 2025. godine, bolesnica je bila subjektivno dobro, a na posljednjem priloženom RTG-u torakalne i lumbosakralne kralježnice nisu opisane nove kompresivne frakture, te je nastavljena supstutucija vitamina D (25 000 IU jednom tjedno).

Rasprava: prema izvješću nekoliko autora, rizični čimbenici za razvoj PLO mogu biti prisutni i u do 80% slučajeva, a jedan od njih je i primjena farmakoterapije koja potiče

gubitak koštane mase kao što su heparin, sistemski glukokortikoidi, analozi GnRH i antikonvulzivi (3). U bolesnica s PLO dokazana je smanjena koštana masa, uz održan broj osteoblasta što govori u prilog mogućem poremećaju njihove funkcije (1, 4). Obzirom na navedeno, teriparatid se čini kao atraktivna opcija za bolesnice s težim oblicima postpartalne osteoporoze (1, 3).

Zaključak: zbog niske incidencije PLO-a, točna patofiziologija nije do kraja razješnjena. Obzirom da ne postoji indikacija za snimanje denzitometrije u premenopauzalnih žena, ne postoje podatci o koštanoj masi u ovih bolesnica prije trudnoće, a dosadašnja istraživanja suglasna su da je PLO je uzrokovan određenim prethodnim stanjem koje sprječava kostur da uspješno podnese izazov trudnoće i dojenja (1, 5).

Ključne riječi: Osteoporoza; Trudnoća; Čimbenici rizika; Prijelomi kralježaka.

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S17 Clinical challenges in the diagnosis, treatment and follow-up of postpartum osteoporosis

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Introduction: Osteoporosis is a chronic progressive metabolic disease of the skeletal system characterized by a decrease in bone mineral density, and is divided into primary and secondary osteoporosis according to etiology. Postpartum osteoporosis, or pregnancy and lactation-associated osteoporosis (PLO), is a form of secondary osteoporosis defined by the occurrence of non-traumatic fractures during the third trimester of pregnancy and/or the first months after childbirth, most often compression vertebral fractures. PLO is extremely rare, with an incidence of about 0.4 per 10,000 women (1, 2).

Case report: This case report presents a female patient, now at the age of 45 years old, who was diagnosed with postpartum osteoporosis at the age of 36 years old after her second birth. The patient had given birth twice so far, the first time in 2008 by emergency cesarean section at 38 weeks of pregnancy, and the second time in 2016 when she gave birth to twins. The patient had four spontaneous abortions prior to her pregnancy, which required additional workup by a transfusion specialist, which determined the factor V Leiden mutation, and she received low-molecular-weight heparin from the 5th week of pregnancy, as recommended by the transfusion specialist, during both pregnancies. Already after the first cesarean section, the patient had pain in her spine, which subsided with regular exercise. After the second birth, the pain intensified and an X-ray of the thoracic and lumbosacral spine was performed, which described anteclinally shaped bodies of Th10 and Th11 and biconcave shaped bodies of Th6, L1, L2, L3 and L4 compression fractures of the vertebral bodies as a result of osteoporosis. The patient was examined by an orthopedist, and for a certain period she was provided with an orthosis, and she also underwent physical rehabilitation. An examination was performed by a clinical pharmacologist, who concluded that the osteoporosis described in the patient was possibly a consequence of long-term use of low-molecular-weight heparin. Teriparatide was included in the therapy, which the patient received for two years, until November 2020, after which only vitamin D substitution was continued. At the last check-up in January 2025, the patient was subjectively well, and the latest X-ray of the thoracic and lumbosacral spine did not describe any new compression fractures, and vitamin D substitution was continued (25,000 IU once a week).

Discussion: According to a report by several authors, risk factors for the development

of PLO may be present in up to 80% of patients, and one of them is the use of pharmacotherapy that promotes bone loss, such as heparin, systemic glucocorticoids, GnRH analogues and anticonvulsants (3). Patients with PLO have been shown to have reduced bone mass, with a maintained number of osteoblasts, which suggests a possible dysorder in their function (1, 4). Given the above, teriparatide seems to be an attractive option for patients with more severe forms of postpartum osteoporosis (1, 3).

Conclusion: Due to the low incidence of PLO, the exact pathophysiology is not fully understood. Since there is no indication for densitometry in premenopausal women, there are no data on bone mass in these patients before pregnancy, and previous studies agree that PLO is caused by a certain pre-existing condition that prevents the skeleton from successfully enduring the challenges of pregnancy and breastfeeding (1, 5).

Keywords: Osteoporosis; Pregnancy; Risk factors; Vertebral fractures.

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S18 Kada mala žlijezda postane veliki problem s kojim se ne susrećemo često

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Uvod s ciljem: Za razliku od multinodozne strume koja se često viđa u ambulantama, karcinom paratireoidne žlijezde je iznimno rijetka maligna bolest čija incidencija iznosi 3.5-5.7/10 000 000. Unatoč tome što čini mali udio među malignim oboljenjima (< 0.005 %), pokazuje sklonost lokalnoj invaziji i udaljenim presadnicama, a osim toga dovodi do teških hiperkalcemija premda je zapravo rijedak uzrok primarnog hiperparatireoidizma, svega u 1-2 % slučajeva. Neki genetički sindromi povezani s hiperparatireoidizmom (sindrom hiperparatireoidizma i tumora čeljusti-HPT-JT sindrom, izolirani obiteljski hiperparatireoidizam te multipla endokrina neoplazija tip 1 i 2A) smatraju se rizičnim čimbenicima za nastanak ovog karcinoma.

Prikaz slučaja: Bolesnica u dobi od 49 godina pratila se 9 godina zbog polinodozne strume te je tijekom tog razdoblja bila eutireoidna. Radi se o pacijentici s arterijskom hipertenzijom zadnjih 10 godina, nefrolitijazom unazad 5 godina, znacima razvitka kronične bubrežne bolesti nerazjašnjene etiologije posljednjih nekoliko mjeseci uz prvu manifestaciju gihta prije 3 mjeseca. S obzirom na djelomično retrosternalno smještenu strumu i njenu progresiju, indicirao se operativni zahvat. Iz učinjenih laboratorijskih serumskih nalaza u sklopu preoperativne obrade izdvajaju se sljedeće vrijednosti: eritrociti 3.45x1012/L, hemoglobin 100 g/L, MCV 87.8 fL, urea 12.6 mmol/L, kreatinin 194 umol/L, kalcij (Ca) 3.79 mmol/L i fosfor 1.07 mmol/L. Nije učinjena vrijednost paratireoidnog hormona. Bolesnica je podvrgnuta zahvatu totalne tireoidektomije koji je protekao uredno kao i rani postoperativni tijek. Na kontrolnom pregledu za tjedan dana žalila se na trnce u području lica i ruku te je obradom potvrđena hipokalcemija (ukupni Ca 1.60 mmol/L, ionizirani Ca 0.89 mmol/L) zbog čega je hospitalizirana. Izmjeren intaktni paratireoidni hormon iznosio je 50 pg/ml. U međuvremenu pristiže patohistološki nalaz materijala uzetog prilikom tireoidektomije kojim se verificiraju karcinom paratireoidne žlijezde te nodozna koloidna struma štitnjače. Gotovo cijeli desni režanj (veličine 6x2.5cm) bio je tumorski promijenjen, s nakupinom tumorskih stanica unutar i izvan čahure te sa znakovima angioinvazije. Dijagnostička obrada bila je proširena radi potvrde eventualno udruženih endokrinoloških poremećaja koji temeljem pristiglih nalaza nisu nađeni. Isto tako, nije otkriveno ni sekundarizama. Tijekom hospitalizacije provođena je parenteralna i peroralna nadoknada Ca te vitamina D uz titraciju supstitucijske terapije levotiroksinom s čime je bolesnica dobrog stanja otpuštena kući urednih vrijednosti elektrolita. Vrijednosti T-score za kralježnicu (-2.7) i kuk (-2.9) govore u prilog osteoporozi.

Konzultiran je operater koji nije nalazio indikaciju za reoperaciju, već je savjetovao daljnje praćenje. Onkolog nije bio uključivan u liječenje bolesnice jer za ovu vrstu karcinoma nije bilo adekvatne adjuvantne terapije (medikamentozna terapija/zračenje). Učinjenim PET-CT-om 2 mjeseca nakon operativnog zahvata nije se našlo znakova lokalnog rediciva niti udaljenih presadnica. Također, isti nalaz opisan je i nakon godinu dana.
Rasprava: Kod bolesnice je uz nalaz polinodozne koloidne strume verificiran i karcinom paratireoidne žlijezde koji je shvaćen kao uzrok prijeoperativne hiperkalcemije. Provedena je supstitucija Ca i vitamina D u sklopu liječenja sindroma «gladnih kostiju» koji je dodatno potenciran i preegzistentnom renalnom disfunkcijom.

Zaključak: Karcinom paratireoidne žlijezde je rijetka maligna bolest s agresivnom prirodom, međutim ako se otkrije u ranom stadiju, operativno liječenje može biti i konačno, uz daljnje praćenje. Treba ga imati na umu kod teške hiperkalcemije i hiperparatireoidizma.

Ključne riječi: hiperkalcemija, karcinom paratireoidne žlijezde, hiperparatireoidizam

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S18 When the small gland becomes a big problem that we do not often meet

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Introduction: Unlike multinodular goiter, which is often seen in hospital, parathyroid carcinoma is an extremely rare malignant disease with an incidence of 3.5-5.7/10,000,000. Despite the fact that it stands for a small proportion of malignant diseases (< 0.005%), it shows a tendency for local invasion and widespread metastatic disease, and in addition leads to severe hypercalcemia, although it is actually a rare cause of primary hyperparathyroidism, only in 1-2% of cases. Some genetic syndromes associated with hyperparathyroidism (hyperparathyroidism-jaw tumor (HPT-JT) syndrome, isolated familial hyperparathyroidism, and multiple endocrine neoplasia type 1 and 2A) are considered as risk factors for the development of this type of cancer.

Case report: A 49-year-old female patient was followed up because of multinodular goiter for 9 years and she was euthyroid during that period. From patient´s medical history: hypertension last 10 years, kidney stones last 5 years, signs of kidney failure unknown etiology last few months with the the first manifestation of gout 3 months ago. Considering the partially retrosternal situated goiter and its progression, surgery was indicated. From the laboratory serum findings as part of the preoperative treatment: erythrocytes 3.45x1012/L, hemoglobin 100 g/L, MCV 87.8 fL, urea 12.6 mmol/L, creatinine 194 umol/L, calcium (Ca) 3.79 mmol/L and phosphorus 1.07 mmol/L. The value of parathyroid hormone was not measured. The patiend underwent a total thyroidectomy, which went smoothly, as did the early postoperative recovery. At the follow-up examination in one week, patient complained of tingling in the face and hands, and hypocalcaemia (total Ca 1.60 mmol/L, ionized Ca 0.89 mmol/L) was confirmed so she was hospitalized. Intact parathyorid hormon was measured 50 pg/ml. In the meantime, the histopatological findings of the material taken during the thyroidectomy were finished, and parathyroid carcinoma and thyroid nodular colloid goiter were verified. Almost the entire right lobe (size 6x2.5cm) was changed by tumor, with a cluster of tumor cells inside and outside the capsule, and with angioinvasion. Diagnostic procedures was expanded to confirm possible associated endocrinological disorders that were not found based on the findings received. Also, no metastases were detected. During hospitalization, parenteral and oral replacement of Ca and vitamin D was performed with titration of levothyroxine substitution therapy, which was therapy the patient was discharged home with, in good condition, and normal electrolyte values. T-score values for the spine (-2.7) and hip (-2.9) condisered osteoporosis. The surgeon was consulted,

with conslusion there is no indication for reoperation, but advised further following up. The oncologist was not involved in the patient´s treatment because there was no adequate adjuvant therapy (drug therapy/radiation) for this type of cancer. A PET-CT performed 2 months after the surgical resection showed no signs of local recurrence or widespread metastatic disease. Also, the same finding was described after one year.

Discussion: In the patient, parathyroid carcinoma was verified along with multinodular goiter, and that carcinoma was considered as the cause of preoperative hypercalcemia. Substitution of Ca and vitamin D was performed as a part of the treatment of «hungry bone» syndrome, which was additionally potentiated by preexisting renal dysfunction. Conclusions: Parathyorid carcinoma is a rare malignant disease with an aggressive potential, however, if detected at an early stage, surgical treatment can be definitive, with further following up. It should be kept in mind in evaluation of severe hypercalcemia and hyperparathyroidism.

Key words: Hypercalcemia, Parathyroid Carcinoma, Hyperparathyroidism

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S19 Primarni hiperparatireoidizam uzrokovan terapijom litijem

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Uvod s ciljem: Paratireoidni hormon (PTH) jedan je od glavnih hormona koji moduliraju homeostazu kalcija i fosfata. U fiziološkim uvjetima, lučenje paratireoidnog hormona uvjetovano je razinom serumskog kalcija. Kod primarnog hiperparatireoidizma dolazi do neprimjerenog lučenja PTH te povišenja serumskog kalcija. Najčešće je asimptomatska bolest, međutim može se manifestirati suptilnim ili nespecifičnim simptomima poput umora, bolova u kostima ili nefrolitijazom. Cilj rada je prikazati slučaj primarnog hiperparatireoidizma kod bolesnice koja je liječena litijem zbog depresije.

Prikaz slučaja: Bolesnica u dobi od 58 godina hospitalizirana je radi dodatne obrade, zbog u više navrata, ambulantno izmjerenih povišenih vrijednosti ukupnog kalcija oko 2.70 mmol/L, ioniziranog kalcija oko 1.50 mmol/L te granično povišenog PTH 7.45 pmol/L. Od komorbiditeta bolesnica je navela paroksizme fibrilacije atrija, lumbosakralni sindrom, depresiju i učestale urinarne infekcije. Za dodati je i nalaz ranije denzitometrije koja ukazuje na osteoporozu kralježnice. U terapiji je koristila: litij karbonat 300 mg 1+1/2+1 tbl., fluvoksamin 100 mg 1 tabletu navečer, flurazepam 1 tabletu po potrebi, bisoprolol 2.5 mg 1 tabletu ujutro, kolekalciferol 25000 i.j. svakih 15 dana 2 ampule i folat 5 mg 1 tabletu ujutro. U statusu nije bilo kliničkih odstupanja. U laboratorijskim nalazima nađene su povišene vrijednosti ukupnog (2.76 mmol/L) i ioniziranog (1.41 mmol/L) kalcija te PTH (9.6 pmol/L), dok je vitamin D bio 81.3 nmol/L. Prikupljen je i uzorak 24-satnog urina u kojem su analizirane vrijednosti kalcija, fosfata, ukupnih proteina i albumina, sve vrijednosti bile su uredne. Učinjena je SPECT scintigrafija vrata i toraksa sestamibijem na kojoj je uočeno intenzivno nakupljanje radiofarmaka uz donji pol lijevog režnja štitnjače, a i nakupljanje u oba režnja štitnjače. Ultrazvukom štitnjače prikaže se uvećana štitnjača difuzno promijenjene ehostrukture, uz donji pol lijevog režnja hipoehogena zona 6 x 4.5 mm koja je punktirana radi određivanja PTH i za citološku analizu, a opisano je i više limfnih čvorova koji se doimaju reaktivni. Nalaz PTH u punktatu bio je 0.5 pmol/L, a u citološkom nalazu opisana je periferna krv i homogena tvar, što ne ukazuje na uvećanu paratireoidnu žlijezdu. Nalaz denzitometrije odgovarao je osteopeniji. Dodatno je učinjen i rentgen torakalne i lumbosakralne kralježnice, prikazana je skolioza s degenerativnim promjenama kralježnice, a bez elemenata kompresivnih fraktura. Bolesnica nije pristala na eventualnu zamjenu litij karbonata drugim antidepresivom te je otpuštena s preporukom nastavka dotadašnje terapije, korigirana je doza kolekaciferola na 25000 i.j. 1 ampula svakih 15 dana, a u terapiju je pridodan sinakalcet 30 mg 2x1 tablete dnevno radi snižavanja vrijednosti kalcija. Bolesnica je kroz kontrole dodatno educirana o pravilnoj primjeni sinakalceta (kako se mora uzimati uz obrok čime se povećava bioraspoloživost)

te se u daljnjim kontrolama prati normalizacija vrijednosti kalcija uz redukciju doze na 30 mg 1 tbl. dnevno. Na zadnjoj kontroli ukupni kalcij je bio 2.35 mmol/L, a PTH 8.5 pmol/L.

Rasprava: Etiologija primarnog hiperparatireoidizma je kompleksna, u literaturi se navode mnoga stanja, lijekovi i mutacije gena koje su povezane s pojavom ove bolesti. Kod ove bolesnice najvjerojatnije se radilo o hiperparatireoidizmu koji je uzrokovan kroničnom terapijom litijem za kojeg je poznato kako može povisiti razinu PTH i kalcija, a patomorfološki supstrat je najčešće hiperplazija paratireoidnih žlijezda.

Zaključak: Ovaj slučaj naglašava složenost dijagnosticiranja etiologije primarnog hiperparatireoidizma te mogućnost liječenja sinakalcetom kada je operativno liječenje neučinkovito. Neliječeni primarni hiperparatireoidizam može dovesti do osteoporoze, bubrežnih kamenaca i kardiovaskularne bolesti. Pristup liječenju u ove bolesnice, koji je uključivao farmakološko liječenje sinakalcetom, pokazao se učinkovitim u stabilizaciji razine kalcija i PTH te prevenciji daljnjih komplikacija. Ovaj slučaj također služi kao podsjetnik na složenu interakciju između lijekova i endokrinološkog sustava, osobito kod bolesnika koji koriste psihofarmake.

Ključne riječi: hiperparatireoidizam, hiperkalcemija, depresija, litij

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S19 Primary hyperparathyroidism caused by lithium therapy

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Introduction with Objective: Parathyroid hormone (PTH) is one of the main hormones that modulate calcium and phosphate homeostasis. Under physiological conditions, the secretion of parathyroid hormone is regulated by serum calcium levels. In primary hyperparathyroidism, there is an inappropriate secretion of PTH, leading to elevated serum calcium levels. It is most often an asymptomatic condition, although it can manifest with subtle or nonspecific symptoms such as fatigue, bone pain, or nephrolithiasis. The aim of this paper is to present a case of primary hyperparathyroidism in a patient who was treated with lithium for depression.

Case Presentation: A 58-year-old female patient was hospitalized for further evaluation due to repeatedly elevated total calcium levels of about 2.70 mmol/L, ionized calcium around 1.50 mmol/L, and borderline elevated PTH (7.45 pmol/L), measured in outpatient settings. Her comorbidities included paroxysmal atrial fibrillation, lumbosacral syndrome, depression, and recurrent urinary infections. Additionally, a prior bone densitometry result indicated osteoporosis of the spine. Her current medications included: lithium carbonate 300 mg 1+1/2+1 tablet, fluvoxamine 100 mg 1 tablet in the evening, flurazepam 1 tablet as needed, bisoprolol 2.5 mg 1 tablet in the morning, cholecalciferol 25,000 IU every 15 days (2 ampoules), and folate 5 mg 1 tablet in the morning. Clinically, no abnormalities were noted. Laboratory tests showed elevated total (2.76 mmol/L) and ionized (1.41 mmol/L) calcium, as well as PTH (9.6 pmol/L), while vitamin D was 81.3 nmol/L. A 24-hour urine sample was collected and analyzed for calcium, phosphate, total proteins, and albumin, all of which were normal. A SPECT scan of the neck and chest with sestamibi revealed intense radioisotope accumulation at the lower pole of the left thyroid lobe, as well as accumulation in both thyroid lobes. Thyroid ultrasound showed an enlarged thyroid with diffusely altered echostructure, and a hypoechoic zone (6 x 4.5 mm) at the lower pole of the left lobe, which was punctured for PTH and cytological analysis. The cytological report described peripheral blood and homogeneous material, not indicating an enlarged parathyroid gland. The bone densitometry results indicated osteopenia. A chest and lumbosacral spine X-ray showed scoliosis with degenerative changes, but no signs of compressive fractures. The patient refused to switch lithium carbonate to another antidepressant and was discharged with recommendations to continue her current therapy, with a corrected dose of cholecalciferol 25,000 IU 1 ampoule every 15 days and the addition of cinacalcet 30 mg 2x1 tablets daily to reduce calcium levels. The patient was further educated on the proper use of cinacalcet (it must be taken with food to increase bioavailability), and subsequent follow-up visits showed

normalization of calcium levels with a reduced dose of 30 mg 1 tablet daily. At the last follow-up, total calcium was 2.35 mmol/L, and PTH was 8.5 pmol/L.

Discussion: The etiology of primary hyperparathyroidism is complex, with many conditions, medications, and gene mutations associated with the development of this disease. In this patient, the most likely cause of hyperparathyroidism was chronic lithium therapy, which is known to increase PTH and calcium levels. The pathological substrate is most often parathyroid gland hyperplasia.

Conclusion: This case highlights the complexity of diagnosing the etiology of primary hyperparathyroidism and the possibility of treating it with cinacalcet when surgical treatment is ineffective. Untreated primary hyperparathyroidism can lead to osteoporosis, kidney stones, and cardiovascular disease. The treatment approach in this patient, which included pharmacological treatment with cinacalcet, was effective in stabilizing calcium and PTH levels and preventing further complications. This case also serves as a reminder of the complex interaction between medications and the endocrine system, particularly in patients using psychotropic drugs.

Keywords: hyperparathyroidism, hypercalcemia, depression, lithium

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S20 Primjena teriparatida u liječenju hipoparatireoidizma s teškom hipokalcemijom: prikaz slučaja

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Uvod s ciljem: Paratireoidni hormon (PTH) jedan je od glavnih hormona koji moduliraju homeostazu kalcija i fosfata. U fiziološkim uvjetima, lučenje paratireoidnog hormona uvjetovano je razinom serumskog kalcija. Primarni hipoparatireoidizam je klinički poremećaj kojeg karakterizira smanjena sekrecija paratireoidnog hormona uslijed poremećaja na razini samih paratireoidnih žlijezda s posljedičnom hipokalcemijom i hiperfosfatemijom. Klinička manifestacija primarnog hipoparatireoidizma ovisi o stupnju hipokalcemije, a obuhvaća neurološke i neuromuskularne simptome. Cilj rada je prikazati primjenu teriparatida u liječenju bolesnika s primarnim hipoparatireoidizmom i teškom hipokalcemijom.

Prikaz slučaja: Bolesnik u dobi od 75 godina inicijalno je hospitaliziran na Zavodu za kardiologiju zbog brze forme fibrilacije atrija i sumnje na akutni koronarni sindrom uz neurološke simptome otežanog govora, nespecifične trnce u tijelu i probadanja u prsištu. U inicijalnim laboratorijskim nalazima izdvajala se teška hipokalcemija (ukupni kalcij 1,07 mmol/L, ionizirani 0,47 mmol/L), snižen magnezij (0,61 mmol/L), povišena vrijednosti fosfata (1,96 mmol/L) i snižen PTH (<0,42 pmol/L). Nakon stabilizacije stanja primjenom parenteralnog kalcija, učinjena je proširena etiološka obrada hipokalcemije na Odjelu za enokrinologiju, dijabetes i bolesti metabolizma kojom je verificiran primarni hipoparatireoidizam, a uz kovencionalnu terapiju hipoparatireoidizma s hipokalcemijom koja je uključivala primjenu kalcijevog karbonata (5x1gr) te kalcitriola (2x0,5ug) postignuta je zadovoljavajuća kontrola elektrolita. Vjerojatni uzrok primarnog hipoparatiroidizma je nedavna endarterektomija desne karotidne arterije. Nakon otpusta iz bolnice bolesnik je ubrzo ponovno hospitaliziran zbog teške hipokalcemije uz vrijednosti ioniziranog kalcija 0,62 mmol/L uslijed neuzimanja preporučene terapije koja je uključivala kalcijev karbonat i kalcitriol. Tijekom druge hospitalizacije bio je ovisan o visokim dozama parenteralnog i peroralnog kalcija, a primjenjene su i maksimalne doze kalcitriola uz dodatak kolekalciferola, indapamida i magnezija. S obzirom na kontinuiranu ovisnost o parenteralnom kalciju i visokim dozama peroralnog kalcija te kalcitriola, nakon pretraživanja literature odlučili smo u terapiju uvesti i teriparatid. Uz svakodnevnu subkutanu primjenu teriparatida u dozi 20 mcg dnevno, nastavak peroralnog unosa kalcija (5x1g), kalcitriola (2x1,0 mcg), kolekalciferola (3600 IU) i magnezija (375mg) prati se poboljšanje kliničkog stanja i laboratorijskih nalaza (ionizirani kalcij 0,97 mmol/L; magnezij 0,66 mmol/L, fosfat 1,12 mmol/L) uz postupno smanjenje doze preparata kalcija na 3x1gr i kalcitriola na 2x0,75 ug.

Rasprava: U do sada objavljenim radovima teriparatid (rhPTH [1-34]) primijenjen subkutano ili putem inzulinske pumpe koristio se u liječenju kroničnog hipoparatiroidizma. Od ostalih analoga PTH na tržištu nije dostupan rhPTH (1-84), a tek nedavno je na tržište došao palopegteriparatid. Kod ranije prikazanog bolesnika odlučili smo se započeti subkutanu primjenu teriparatida uz peroralni kalcij i kalcitriol, a u kontrolnim nalazima u 17. danu primjene postignuta je zadovoljavajuća vrijednosti ukupnog kalcija (2,23 mmol/L), porast vrijednosti ioniziranog kalcija (1,12 mmol/L) te zadovoljavajuća vrijednost fosfata (1,22 mmol/L). S obzirom na kratak vremenski period praćenja, u daljnjem tijeku liječenja u slučaju neadekvatne kontrole elektrolita preostali modaliteti su: intenziviranje subkutane primjene teriparatida u većoj dozi ili primjena teriparatida putem inzulinske pumpe, a razmatra se i liječenje palopegteriparatidom.

Zaključak: Konvencionalno liječenje kroničnog primarnog hipoparatiroidizma kalcijem i kalcitriolom ne omogućuje uvijek adekvatan klinički i biokemijski odgovor. Primjena rekombinantnog humanog PTH-teriparatida predstavlja mogućnost liječenja kroničnog hipoparatiroidizma u bolesnika koji nisu adekvatno kontroliralni konvencionalnom terapijom no podatci su ograničeni i potrebna su daljnja istraživanja. U ovom prikazu slučaja naš je bolesnik uz subkutanu primjenu teriparatida s kalcitriolom i peroralnim kalcijem postigao zadovoljavajuću kontrolu elektrolita.

Ključne riječi: hipoparatireoidizam, hipokalcemija, hiperfosfatemija, hipomagnezemija, teriparatid.

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S20 Use of teriparatide in the treatement of primary hypoparathyreoidism with severe hypocalcemia: Case report

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Introduction: Parathyroid hormone (PTH) is one of the key hormones that regulate calcium and phosphate homeostasis. Under physiological conditions, the secretion of parathyroid hormone is determined by serum calcium levels. Primary hypoparathyroidism is a clinical disorder characterized by reduced secretion of parathyroid hormone due to dysfunction at the level of the parathyroid glands, resulting in hypocalcemia and hyperphosphatemia. The clinical manifestation of primary hypoparathyroidism depends on the severity of hypocalcemia and includes neurological and neuromuscular symptoms. The aim of this paper is to present the application of teriparatide in the treatment of patients with primary hypoparathyroidism and severe hypocalcemia.

Case report: A 75-year-old patient was initially hospitalized in the Department of Cardiology due to rapid atrial fibrillation and suspected acute coronary syndrome, along with neurological symptoms including speech difficulties, nonspecific tingling sensations in the body, and chest pain. Initial laboratory findings revealed severe hypocalcemia (total calcium 1.07 mmol/L, ionized calcium 0.47 mmol/L), decreased magnesium levels (0.61 mmol/L), elevated phosphate levels (1.96 mmol/L), and low PTH (<0.42 pmol/L). After stabilizing the condition with parenteral calcium administration, an extended etiological evaluation of hypocalcemia was conducted in the Department of Endocrinology, Diabetes, and Metabolic Diseases, confirming primary hypoparathyroidism. Conventional therapy for hypoparathyroidism with hypocalcemia, which included calcium carbonate (5x1g) and calcitriol (2x0.5 µg), resulted in satisfactory electrolyte control. The likely cause of primary hypoparathyroidism was a recent right carotid endarterectomy. Shortly after hospital discharge, the patient was readmitted due to severe hypocalcemia (ionized calcium 0.62 mmol/L) following noncompliance with the recommended therapy, which included calcium carbonate and calcitriol. During the second hospitalization, the patient was dependent on high doses of parenteral and oral calcium, with maximum doses of calcitriol, along with additional supplementation of cholecalciferol, indapamide, and magnesium. Given the continuous dependence on parenteral calcium and high doses of oral calcium and calcitriol, a literature review led to the decision to introduce teriparatide into the treatment regimen. With daily subcutaneous administration of teriparatide at a dose of 20 mcg/day, continued oral calcium intake (5x1g), calcitriol (2x1.0 µg),

cholecalciferol (3600 IU), and magnesium (375 mg), an improvement in clinical condition and laboratory findings was observed (ionased calcium 0.97 mmol/L; Magnesium 0.66 mmol/L; phosphate 1.12 mmol/L). This allowed for a gradual reduction in calcium supplementation to 3x1g and calcitriol to 2x0.75 µg.

Discussion: In previously published studies, teriparatide (rhPTH [1-34]), administered subcutaneously or via an insulin pump, has been used in the treatment of chronic hypoparathyroidism. Among other PTH analogs, rhPTH (1-84) is not available on the market, while palopegteriparatide has only recently become commercially available. For the previously presented patient, we decided to initiate subcutaneous administration of teriparatide alongside oral calcium and calcitriol. By the 17th day of treatment, follow-up laboratory results showed satisfactory total calcium levels (2.23 mmol/L), an increase in ionized calcium levels (1.12 mmol/L), and satisfactory phosphate levels (1.22 mmol/L). Given the short follow-up period, if electrolyte control proves inadequate in the course of further treatment, the remaining options include intensifying the subcutaneous administration of teriparatide at a higher dose, administering teriparatide via an insulin pump, or considering treatment with palopegteriparatide.

Conclusion: Conventional treatment of chronic primary hypoparathyroidism with calcium and calcitriol does not always ensure an adequate clinical and biochemical response. The use of recombinant human PTH-teriparatide offers a treatment option for chronic hypoparathyroidism in patients who are not adequately controlled with conventional therapy; however, data are limited, and further research is needed. In this case report, our patient achieved satisfactory electrolyte control with subcutaneous administration of teriparatide in combination with calcitriol and oral calcium.

Keywords: hypoparathyroidism, hypocalcemia, hyperphosphatemia, hypomagnesemia, teriparatide.

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REPRODUKTIVNI SUSTAV

S21 Jednostavna virilizirajuća kongenitalna adrenalna hiperplazija: Dijagnostički izazovi i pristup liječenju u trudnoći – prikaz slučaja

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Uvod s ciljem: Kongenitalna adrenalna hiperplazija (CAH) skupina je autosomno recesivnih poremećaja uzrokovanih enzimskim deficitima u steroidogenezi nadbubrežnih žlijezda, što rezultira smanjenom sintezom kortizola i aldosterona te kompenzacijskim povećanjem androgena. Najčešći uzrok je deficit 21-hidroksilaze (21-OHD), koji čini preko 90 % slučajeva. Jednostavna virilizirajuća kongenitalna adrenalna hiperplazija (SV-CAH) predstavlja oblik CAH-a karakteriziran značajnim deficitom enzima, što dovodi do izraženog hiperandrogenizma, ali bez poremećaja ravnoteže elektrolita. Za razliku od teže forme klasičnog CAH-a, ne uzrokuje adrenalnu krizu u neonatalnom razdoblju, već se najčešće očituje u djetinjstvu i adolescenciji. Procijenjena prevalencija SV-CAH-a znatno je niža u odnosu na neklasični oblik CAH-a te iznosi oko 1:15 000. Zbog preklapanja simptoma, SV-CAH se ponekad pogrešno dijagnosticira kao sindrom policističnih jajnika (PCOS), što može odgoditi postavljanje točne dijagnoze.

Prikaz slučaja: Prikazujemo 28-godišnju bolesnicu upućenu od ginekologa zbog progresivnog hirzutizma tijekom posljednja tri mjeseca, uz iregularne menstrualne cikluse. Bolesnica je prethodno 11 godina uzimala oralnu hormonsku kontracepciju radi PCOS tijekom koje su ciklusi bili uredni te je subjektivno bila bez smetnji. Klinički status bolesnice bio je bez osobitosti. Učinjenom endokrinološkom obradom zabilježene su značajno povišene vrijednosti testosterona (5,26 nmol/L, ref. 0,07-1,56 nmol/L), 17-hidroksiprogesterona (32,08 nmol/L, ref. < 5,60 nmol/L) i androstendiona (19,48 nmol/L, ref. 1,22-8,73 nmol/L). Vrijednosti LH, FSH, estradiola i prolaktina bile su unutar referentnih granica, dok su ostali nalazi učinjene obrade prikazani u Tablici 1. Dodatno je učinjen stimulacijski ACTH test s 250 mcg s određivanjem 17-OHP i kortizola čime je potvrđena dijagnoza NCAH te isključena adrenalna insuficijencija (Tablica 2). Magnetska rezonanca nadbubrežnih žlijezda pokazala je uredan nalaz. Genetskim testiranjem potvrđeno je da je bolesnica složeni heterozigot za mutacije CYP21A2 c.844G>T, p.(Val282Leu) i CYP21A2 c.1069C>T, p.(Arg357Trp), dok su nalazi partnerovog testiranja bili uredni. Tijekom dijagnostičke obrade bolesnica je spontano ostala trudna. S obzirom da je mutacija CYP21A2 c.1069C>T, p.(Arg357Trp) dovodi do značajnog smanjenja enzimske aktivnosti te uzimajući u obzir značajno povišene razine androgena,

postavljena je dijagnoza SV-CAH te je u terapiju uveden hidrokortizon u dozi 5 mg ujutro, 2,5 mg poslijepodne i 5 mg navečer. Daljnje endokrinološko i ginekološko praćenje usmjereno je na prilagodbu nadomjesne terapije prema potrebama trudnoće i prevenciji potencijalnih komplikacija.

Rasprava: SV-CAH obično se dijagnosticira u djetinjstvu zbog znakova hiperandrogenizma, uključujući ubrzan rast, prijevremeno zatvaranje epifiza ili blagu klitoromegaliju. U adolescenciji i odrasloj dobi očituje se izraženim hirzutizmom, aknama i iregularnim mensturalnim ciklusima. Kod naše bolesnice dijagnoza je je odgođena zbog rezidualne aktivnosti 21-OH i dugotrajne primjene hormonske kontracepcije koja je suprimirala androgene i održavala uredne menstrualne cikluse. Genetska analiza pokazala je kombinaciju mutacija p.Val282Leu i p.Arg357Trp, pri čemu potonja mutacija dovodi do značajnog smanjenja enzimske aktivnosti, no unatoč tome, prenatalna androgenizacija nije bila dovoljno izražena da bi uzrokovala ambigvitet vanjskog spolovila, što dodatno otežava ranu dijagnozu.

Zaključak: SV-CAH i NCAH predstavljaju važan diferencijalnodijagnostički entitet u žena s hiperandrogenizmom i menstrualnim poremećajima. Pravovremena sumnja na ovu dijagnozu, temeljena na anamnezi i kliničkoj slici, ključna je za rano prepoznavanje bolesti. Endokrinološka obrada i genetsko testiranje nužni su za postavljanje točne dijagnoze i prevenciju mogućih komplikacija, osobito u trudnoći. Trudnoća kod ovih bolesnica zahtijeva sustavno endokrinološko i ginekološko praćenje radi prilagodbe nadomjesne terapije i smanjenja rizika od fetalne androgenizacije.
Ključne riječi: Jednostavna virilizirajuća kongenitalna adrenalna hiperplazija; Poremećaji steroidogeneze; Genetsko testiranje; Endokrine komplikacije u trudnoći

Tablica 1. Nalazi učinjene endokrinološke obrade

Hormon	Vrijednost	Referentni interval
Kortizol	437 nmol/L	101-536 nmol/L
11-deoksikortizol	4,89 nmol/L	< 3,09 nmol/L
17-hidroksiprogesteron	32,08 nmol/L	< 5,60 nmol/L
Aldosteron	419 pmol/L	32-654 pmol/L
Testosteron	5,26 nmol/L	0,07-1,56 nmol/L
Udio slobodnog testosterona	0,9 %	0,5 – 2 %
DHEAS*	7,33 umol/L	1,19-8,04 umol/L
Androstendion	21,98 nmol/L	1,22-8,73 nmol/L
ACTH**	20,5 pmol/L	1,6-13,9 pmol/L

*Dehidroepiandrosteron sulfat, **Adrenokortikotropni hormon

Tablica 2. 17-hidroksiprogestron i kortizol u stimulacijskom ACTH testu s 250 mcg

Hormon	0 min	30 min	60 min
Kortizol	437 nmol/L	479 nmol/L	491 nmol/L
17 - OHP*	94,43 nmol/L	157,89 nmol/L	168,42 nmol/L

*17-hidroksiprogesteron

Literatura: [1] Auer MK, Nordenström A, Lajic S, Reisch N. Congenital adrenal hyperplasia. Lancet. 2023 Jan 21;401(10372):227-244. doi: 10.1016/S0140-6736(22)01330-7. Epub 2022 Dec 8. PMID: 36502822.; [2] Carmina E, Dewailly D, Escobar-Morreale HF, Kelestimur F, Moran C, Oberfield S, Witchel SF, Azziz R. Non-classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency revisited: an update with a special focus on adolescent and adult women. Hum Reprod Update. 2017 Sep 1;23(5):580-599. doi: 10.1093/humupd/dmx014. PMID: 28582566.; [3] Singh R, Agarwal M, Sinha S. Challenges in the Diagnosis of Simple-Virilizing Congenital Adrenal Hyperplasia: A Case Report. Cureus. 2022 Oct 5;14(10):e29966. doi: 10.7759/cureus.29966. PMID: 36225242; PMCID: PMC9535115.; [4] Tankoska M, Anastasovska V, Krstevska-Konstantinova M, Naydenov M, Kocova M. Therapeutic challenges in a patient with the simple virilizing (SV) form of congenital adrenal hyperplasia (CAH) due to the P30L/I172N genotype. J Pediatr Endocrinol Metab. 2019 May 27;32(5):543-547. doi: 10.1515/jpem-2018-0285. PMID: 31026224.

S21 Simple Virilizing Congenital Adrenal Hyperplasia: Diagnostic Challenges and Pregnancy Management – A Case Report

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Introduction and Objective: Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders caused by enzyme deficiencies in adrenal steroidogenesis, leading to impaired cortisol and aldosterone synthesis and compensatory androgen excess. The most common cause of CAH is 21-hydroxylase deficiency (21-OHD), accounting for over 90 % of cases. Simple virilizing congenital adrenal hyperplasia (SV-CAH) is a form of CAH characterized by a significant enzyme deficiency, leading to pronounced hyperandrogenism but without electrolyte imbalance. Unlike the more severe salt-wasting form of classic CAH, it does not cause an adrenal crisis in the neonatal period but typically manifests in childhood or adolescence. The estimated prevalence of SV-CAH is significantly lower than that of the non-classic form, approximately 1:15,000. Due to overlapping symptoms, SV-CAH is sometimes misdiagnosed as polycystic ovary syndrome (PCOS), which can delay an accurate diagnosis.

Case Report: We present a 28-year-old female referred by a gynecologist due to progressive hirsutism over the past three months and irregular menstrual cycles. The patient had previously taken oral hormonal contraception for 11 years for PCOS, during which her cycles remained regular, and she was asymptomatic. Clinical examination was unremarkable. Endocrinological evaluation revealed significantly elevated testosterone (5.26 nmol/L, ref. 0.07–1.56 nmol/L), 17-hydroxyprogesterone (32.08 nmol/L, ref. <5.60 nmol/L), and androstenedione (19.48 nmol/L, ref. 1.22–8.73 nmol/L). LH, FSH, estradiol, and prolactin levels were within reference ranges, with other findings presented in Table 1. An ACTH stimulation test using 250 mcg, measuring 17-OHP and cortisol, confirmed the diagnosis of SV-CAH and ruled out adrenal insufficiency (Table 2). MRI of the adrenal glands showed no abnormalities. Genetic testing confirmed that the patient was a compound heterozygote for CYP21A2 mutations c.844G>T, p.(Val282Leu), and CYP21A2 c.1069C>T, p.(Arg357Trp), while her partner's genetic results were normal. During the diagnostic workup, the patient spontaneously conceived. Given that the CYP21A2 c.1069C>T, p.(Arg357Trp) mutation leads to a significant reduction in enzyme activity and considering the markedly elevated androgen levels, a diagnosis of SV-CAH

was established, and hydrocortisone therapy was introduced at a dose of 5 mg in the morning, 2.5 mg in the afternoon, and 5 mg in the evening. Further endocrinological and gynecological follow-up was aimed at adjusting replacement therapy according to pregnancy needs and preventing potential complications.

Discussion: SV-CAH is typically diagnosed in childhood due to signs of hyperandrogenism, including rapid growth, premature epiphyseal closure, or mild clitoromegaly. In adolescence and adulthood, it is recognized through pronounced hirsutism, acne, and menstrual irregularities. In our patient, the diagnosis was delayed due to residual 21-hydroxylase activity and long-term use of hormonal contraception, which suppressed androgens and maintained regular menstrual cycles. Genetic analysis revealed a combination of p.Val282Leu and p.Arg357Trp mutations, with the latter significantly reducing enzyme activity. Despite this, prenatal androgenization was not sufficient to cause ambiguous genitalia, further complicating early diagnosis.
Conclusion: SV-CAH and NCAH represent important differential diagnoses in women with hyperandrogenism and menstrual disorders. Early suspicion based on history and clinical presentation is crucial for timely disease recognition. Endocrinological evaluation and genetic testing are essential for establishing an accurate diagnosis and preventing potential complications, particularly in pregnancy. Pregnancy in these patients requires systematic endocrinological and gynecological monitoring to adjust replacement therapy and reduce the risk of fetal androgenization.

Keywords: Simple-virilizing congenital adrenal hyperplasia; Steroidogenesis disorders; Genetic testing; Endocrine complications in pregnancy

Table 1. Endocrinological Evaluation Results

Hormone	***Value***	***Reference Range***
Cortisol	*437 nmol/L*	*101-536 nmol/L*
11-Deoxycortisol	*4,89 nmol/L*	*< 3,09 nmol/L*
17-Hydroxyprogesterone	*32,08 nmol/L*	*< 5,60 nmol/L*
Aldosterone	*419 pmol/L*	*32-654 pmol/L*
Testosterone	*5,26 nmol/L*	*0,07-1,56 nmol/L*
Free Testosterone Ratio	*0,9 %*	*0,5 – 2 %*
*DHEAS**	*7,33 umol/L*	*1,19-8,04 umol/L*
Androstenedione	*21,98 nmol/L*	*1,22-8,73 nmol/L*
*ACTH***	*20,5 pmol/L*	*1,6-13,9 pmol/L*

*Dehydroepiandrosterone sulfate, **Adrenocorticotropic hormone

Table 2. 17-OHP and Cortisol in ACTH Stimulation Test

Hormone	***0 min***	***30 min***	***60 min***
Cortisol	*437 nmol/L*	*479 nmol/L*	*491 nmol/L*
17-Hydroxyprogesterone	*94,43 nmol/L*	*157,89 nmol/L*	*168,42 nmol/L*

*17-hidroksiprogesteron

Literature: [1] Auer MK, Nordenström A, Lajic S, Reisch N. Congenital adrenal hyperplasia. Lancet. 2023 Jan 21;401(10372):227-244. doi: 10.1016/S0140-6736(22)01330-7. Epub 2022 Dec 8. PMID: 36502822.; [2] Carmina E, Dewailly D, Escobar-Morreale HF, Kelestimur F, Moran C, Oberfield S, Witchel SF, Azziz R. Non-classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency revisited: an update with a special focus on adolescent and adult women. Hum Reprod Update. 2017 Sep 1;23(5):580-599. doi: 10.1093/humupd/dmx014. PMID: 28582566.; [3] Singh R, Agarwal M, Sinha S. Challenges in the Diagnosis of Simple-Virilizing Congenital Adrenal Hyperplasia: A Case Report. Cureus. 2022 Oct 5;14(10):e29966. doi: 10.7759/cureus.29966. PMID: 36225242; PMCID: PMC9535115.; [4] Tankoska M, Anastasovska V, Krstevska-Konstantinova M, Naydenov M, Kocova M. Therapeutic challenges in a patient with the simple virilizing (SV) form of congenital adrenal hyperplasia (CAH) due to the P30L/I172N genotype. J Pediatr Endocrinol Metab. 2019 May 27;32(5):543-547. doi: 10.1515/jpem-2018-0285. PMID: 31026224.

S22 Debljina kao kontraindikacija u postupcima medicinski pomognute oplodnje

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Uvod s ciljem: Prekomjerna tjelesna masa može negativno utjecati na kvalitetu jajnih stanica, ovulaciju i ukupnu plodnost. Istraživanja pokazuju da žene s viškom kilograma često imaju nepravilne menstrualne cikluse i smanjenu učestalost ovulacije, što može otežati začeće. Stoga je važno da žene koje se podvrgavaju medicinskoj pomoći uz pomoć oplodnje (MPO) održavaju optimalnu tjelesnu masu prije i tijekom postupka.

Prikaz slučaja: Prikazuje se 26-godišnja bolesnica koja neuspješno pokušava začeti 6 godina te se u 03/2017 javlja u ambulantu Zavoda za humanu reprodukciju i medicinski pomognutu oplodnju KBC Osijek. Pri pregledu navodi neredovite menstrualne cikluse, a u kliničkom statusu ističe se povišen ITM koji iznosi 41 kg/m2. Iz medicinske dokumentacije je vidljivo kako je bolesnica eutireoidna uz blago povišen TSH (5,77 mIU/L). Savjetuje se dodatna hormonska obrada, pregled tireologa i redukcija tjelesne mase do ciljne vrijednosti ITM < 30 kg/m2, kada se po protokolima može razmotriti MPO. U 05/2017 na kontrolnom pregledu njezin ITM iznosi 34 kg/m2, a u laboratorijskim nalazima zabilježeni su TSH 3,97 mIU/L, prolaktin 194,5 mIU/L (referentna vrijednost iznosi 109 do 554 mIU/L), progesteron 0,7 nmol/L (referentna vrijednost iznosi < 1 nmol/L) (anovulatio) te se uvodi metformin uz preporuku daljnje redukcije tjelesne mase. Na kontrolnom pregledu u 11/2017 bolesnica ima ITM 28 kg/m2, redovito koristi propisanu terapiju (levotiroksin, metformin, mioinozitol, folacin) te se započinje s protokolima MPO (tzv „štoperica" rekombinantni hCG i pročišćeni hCG za postizanje ovulacije). Nakon postupka inseminacije kao dodatna potpora koristi se sintetski progesteron. U 01/2018 dolazi na očitanje beta HCG koji je pozitivan i iznosi 261,0 IU/L, a ITM iznosi 27,2 kg/m2 te se savjetuje održavanje tjelesne mase uz ranije preporučenu terapiju. Bolesnica se u 08/2018 u 39. tjednu trudnoće (+ 7 kg) javlja na Kliniku radi trudova i dovršetka trudnoće. Porođeno je živo rođeno dijete, PM 2790 g, PD 48 cm AS 10/10.

Rasprava: Liječnici i zdravstveno osoblje mogu pomoći u određivanju optimalne tjelesne mase te preporučiti učinkovite strategije za njezino postizanje i održavanje, uključujući

savjete o prehrani i tjelesnoj aktivnosti. Održavanjem ciljane tjelesne mase lakše se određuju točne doze lijekova u postupcima MPO-a.

Zaključak: Održavanje zdrave tjelesne mase ne samo da povećava izglede za uspjeh medicinski pomognute oplodnje, već i doprinosi općem zdravlju i dobrobiti tijekom cijelog postupka.

Ključne riječi: debljina, MPO, redukcija tjelesne mase, trudnoća

Literatura: [1] **Šimunić V. Reprodukcijska endokrinologija i neplodnost, Medicinski pomognuta oplodnja, IVF. Školska knjiga; 2012.;** [2] **Dornelles VC, Hentschke MR, et.al. The impact of body mass index on laboratory, clinical outcomes and treatment costs in assisted reproduction: a retrospective cohort study. BMC Women´s health. 2022. doi: 10.1186/s12905-022-02036-x;** [3] **Shen X, Li M, et.al. The PPOS protocol mitigates the detrimental effects of high BMI on embryo and clinical pregnancy outcomes. Reproductive Biology and Endocrinology. 2024. doi: 10.1186/s12958-024-01294-8;** [4] **Jeong HG, Cho S, et.al. Effect of weight loss before in vitro fertilization in women with obesity or overweight and infertility: a systematic review and meta-analysis. Scientific Reports. 2024. doi: s41598-024-56818-4**

S22 Obesity as a Contraindication in Medically Assisted Reproduction Procedures

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Introduction: Excess body weight can negatively affect oocyte quality, ovulation, and overall fertility. It has been documented that overweight women are more likely to have irregular menstrual cycles and lower frequency of ovulation, which in turn reduce their chances of conceiving. Thus, optimal body weight among women undergoing MAR is important even before the beginning of the procedure.

Case Report: A 26-year-old patient who had been trying to conceive unsuccessfully for six years presented at the Department of Human Reproduction and Medically Assisted Reproduction at UHC Osijek in March 2017. She complained of irregular menstrual cycles and on clinical examination an increased BMI of 41 kg/m² was noted. Her medical records indicated euthyroidism with slightly elevated TSH (5.77 mIU/L). Further hormonal evaluation, an endocrinology consultation, and weight reduction to a target BMI of <30 kg/m² were recommended before considering MAR protocols. At a follow-up in May 2017, her BMI had decreased to 34 kg/m², with laboratory results showing TSH 3.97 mIU/L, prolactin 194,5 mIU/L (reference value 109 to 554 mIU/L), progesterone 0,7 nmol/L (reference value < 1 nmol/L) (anovulation). Metformin was introduced, and further weight reduction was advised. By November 2017, the patient´s BMI had increased to 28 kg/m², and she regularly took the prescribed therapy, levothyroxine, metformin, myo-inositol, folic acid. MAR treatment commenced, including ovulation induction with recombinant and purified hCG. Following insemination, synthetic progesterone was administered for luteal support. In January 2018, beta-hCG testing was positive at 261.0 IU/L, with a BMI of 27.2 kg/m², and weight maintenance alongside previous therapy was recommended. In August 2018, at a pregnancy week of 39 weeks (+7 kg weight increase), she was admitted for labor. She delivered a healthy newborn, birth weight 2790 g, length 48 cm, Apgar score 10/10.

Discussion: Physicians and health professionals are in a strategic position to advise patients about the achievement of an optimal body weight by proposing dietary and physical activity recommendations. Maintaining a target BMI facilitates precise medication dosing in MAR procedures, improving treatment outcomes.

Conclusion: Maintaining a healthy body weight enhances the success rates of medically assisted reproduction and overall health and well-being during treatment.

Keywords: obesity, medically assisted reproduction, weight reduction, pregnancy.

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DIJABETES I METABOLIZAM

S23 Uzroci kliničke inercije u propisivanju novih antidijabetika: praksa, iskustva i stavovi liječnika obiteljske medicine u Hrvatskoj

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Uvod s ciljem: Zahvaljujući novim antidijabeticima, inhibitorima suprijenosnika natrija-glukoze 2 (SGLT2i) i agonistima GLP-1 receptora (GLP-1 RA), liječenje dijabetesa tipa 2 (DT2) danas prolazi renesansu. Raniji glukocentrični pristup s primarnim ciljem regulacije glikemije, zadnjih desetljeća nadopunio je sveobuhvatniji, dualni pristup, koji istovremeno stavlja naglasak na smanjenje kardiovaskularnog (KV) rizika. Unatoč dokazanim benefitima, recentna istraživanja u svijetu ukazuju na njihovu nedovoljnu propisivanost, zbog utjecaja različitih faktora, okupljenih pod zajednički nazivnik kliničke inercije. Cilj ovog istraživanja bio je utvrditi povezanost prepreka (uzroka inercije) s kojima se liječnici opće/obiteljske medicine (LOM) susreću u procesu propisivanja s njihovom razinom samopouzdanja pri samostalnom propisivanju ovih lijekova.

Metode: Predmet ovog istraživanja je samostalno dizajnirani upitnik koji je dostavljen na e-adrese ordinacija LOM na području cijele Hrvatske u digitalnom formatu. Upitnik je u potpunosti anoniman, namijenjen isključivo LOM. Egzaktne podatke o ukupnom broju pacijenata s dijagnozom DT2 te s propisanim novim antidijabeticima ispitanici su provjerili u e-kartonima. Pitanja o razini samopouzdanja u propisivanju navedenih skupina lijekova postavljena su u obliku Likertove ljestvice, a procjena utjecaja čimbenika na vjerojatnost lošijeg samopouzdanja učinjena je bivarijantnom i multivarijantnom logističkom regresijom.

Rezultati: Istraživanje je provedeno na 168 LOM, od kojih su 66,1 % žene, 49,4 % specijalisti obiteljske medicine, 67,9 % radi u gradskoj sredini. Ukupan broj pacijenata s DT2 je 23 036, među kojima je najveći udio onih u dobi od 60 do 80 godina (57,1 %). S obzirom na prevalenciju KV komplikacija pacijenata s DT2, udio bolesnika s hipertenzijom iznosi 59,1 %, s koronarnom arterijskom bolešću 16,9 % te s bubrežnim popuštanjem (eGFR < 60 mL/min) 13,3 %. Udio DT2 bolesnika koji imaju propisan inhibitor dipeptidil peptidaze 4 (DPP4i) iznosi 33,3 %, SGLT2i 18,6 % te GLP-1 RA 12,1 %. S obzirom na procjenu samopouzdanja, 76,2 % navodi da ima visoku razinu samopouzdanja za propisivanje SGLT2i, a GLP-1 RA 53,6 %. Veće samopouzdanje pri propisivanju SGLT2i ($P = 0,03$) i GLP-1 RA ($P = 0,02$) imaju značajnije više specijalisti obiteljske medicine. Najznačajniji faktori koji su bivarijantnom logističkom regresijom uočeni kao prediktori nižeg samopouzdanja u propisivanju ovih lijekova odnose se na nepoznavanje i kompliciranost smjernica. Multivarijantnom regresijom su pak uočeni modeli koji

smanjuju mogućnost nižeg samopouzdanja; detaljna informiranost o nuspojavama ovih lijekova, te veći broj pacijenata s već propisanim istim lijekom.

Zaključak: Detektiranje prepreka koje uzrokuju kliničku inerciju LOM u propisivanju novih antidijabetika, zbog njihovih KV i nefroloških benefita, ključ je za optimizaciju njihova propisivanja i procesa skrbi o pacijentima s DT2.

Ključne riječi: dijabetes tip 2, SGLT2i, GLP-1 RA, liječnici obiteljske medicine, kliničke smjernice

Literatura: [1] Kurevija T, Šojat D, Bosnić Z, Mujaj B, Canecki Varžić S, Majnarić Trtica L. The Reasons for the Low Uptake of New Antidiabetic Drugs with Cardiovascular Effects-A Family Doctor Perspective. J Clin Med. 2024;13(6):1617. doi:10.3390/jcm13061617.; [2] Davies MJ, Aroda VR, Collins BS, et al. Management of Hyperglycemia in Type 2 Diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2022;45(11):2753-2786. doi:10.2337/dci22-0034.; [3] Khunti, K.; Jabbour, S.; Cos, X.; Mudaliar, S.; Mende, C.; Bonaca, M.; Fioretto, P. Sodium-Glucose Co-Transporter-2 Inhibitors in Patients with Type 2 Diabetes: Barriers and Solutions for Improving Uptake in Routine Clinical Practice. Diabetes Obes. Metab. 2022, 24, 1187–1196.

S23 Clinical inertia in prescribing novel antidiabetics: practice, attitudes and experiences of GPs in Croatia

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Introduction and aim: Thanks to novel antidiabetic medications, sodium-glucose cotransporter 2 inhibitors (SGLT2i) and GLP-1 receptor agonists (GLP-1 RA), the treatment of type 2 diabetes (T2D) is currently undergoing a renaissance. The previous glucocentric approach with the primary goal of glycemic control has been supplemented in recent decades by a more comprehensive, dual approach, which simultaneously emphasizes the reduction of cardiovascular (CV) risk. Despite the proven benefits, recent research worldwide indicates that they are under-prescribed, due to the influence of various factors, assembled into the common denominator of clinical inertia. The aim of this study was to determine the association between the barriers (causes of inertia) that general practitioners (GPs) encounter in the prescribing process and their level of self-confidence in prescribing these medications.

Methods: The subject of this research is a self-designed questionnaire that was delivered to the e-mail addresses of GP´s practices throughout Croatia in digital format. The questionnaire is completely anonymous, intended exclusively for GPs. The respondents checked the exact data on the total number of patients diagnosed with T2D and prescribed novel antidiabetics in their e-database. Questions about the level of self-confidence in prescribing the mentioned groups of medications were asked in the form of a Likert scale, and the assessment of the influence of factors on the probability of poor self-confidence was made using bivariate and multivariate logistic regression.
Results: 168 GPs were examined, of which 66.1% were women, 49.4% were family medicine (FM) specialists, and 67.9% worked in urban areas. The total number of patients with T2D was 23036, with the largest proportion being those aged 60 to 80 years (57.1%). Regarding the prevalence of CV complications in T2D patients, the proportion of patients with hypertension was 59.1%, with coronary artery disease 16.9%, and with renal failure (eGFR < 60 mL/min) 13.3%. The proportion of T2D patients prescribed a dipeptidyl peptidase 4 inhibitor (DPP4i) was 33.3%, SGLT2i 18.6%, and GLP-1 RA 12.1%. Regarding the assessment of self-confidence, 76.2% declared a high level of self-confidence in prescribing SGLT2i, and 53.6% in prescribing GLP-1 RA. FM specialists showed significantly higher self-confidence in prescribing both SGLT2i ($P = 0.03$) and GLP-1 RA ($P = 0.02$). The most significant factors identified by bivariate logistic regression as predictors of lower self-confidence in prescribing these medications were related to lack of knowledge and complexity of guidelines.

Multivariate regression, however, identified models that reduce the possibility of lower self-confidence; detailed information about the side effects of these drugs, and a higher number of patients already prescribed the same drug.

Conclusion: Detecting the barriers that cause clinical inertia of GPs in prescribing novel antidiabetics, due to their CV and nephrological benefits, is key to optimizing their prescribing and the care process for patients with T2D.

Keywords: type 2 diabetes, SGLT2i, GLP-1 RA, family physicians, clinical guidelines

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S24 Izazovi u kvaliteti života sa osteogenesis imperfektom – prikaz slučaja novootkrivenog autoimunog dijabetesa

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Uvod s ciljem: Osteogenesis imperfekta (OI) genetski je poremećaj vezivnog tkiva uzrokovan abnormalnostima u sintezi kolagena tipa I. Kliničke manifestacije variraju od blagih, gotovo asimptomatskih oblika do teških oblika povezanih s visokim perinatalnim mortalitetom. Osim prijeloma, tijek bolesti može biti praćen niskim rastom, deformitetom kostura i hipermobilnošću zglobova. Pojava šećerne bolesti rijedak je, ali ozbiljan komorbiditet u bolesnika sa OI.

Prikaz slučaja: Prikazujemo slučaj 61-godišnjeg bolesnika dovezenog u hitnu neurološku ambulantu radi suspektnog moždanog udara. Heteroanamnestički saznaje se da se bolesnik unazad dva dana žalio na difuznu glavobolju praćenu otežanim izgovaranjem riječi. Iz osobne anamneze ističe se dijagnoza OI postavljena u djetinjstvu, u sklopu koje je zbog opsežnih promjena na ekstremitetima bolesnik nepokretan. Hitno je učinjen CT mozga kojim se isključi akutno neurološko zbivanje. U laboratorijskim nalazima prati se metabolička acidoza s hiperglikemijom uz povišene upalne parametre. Na rendgenskoj snimci srca i pluća opisana je pneumonija bazalno lijevo. Bolesnik je smješten u jedinicu intenzivnog liječenja radi liječenja dijabetičke ketoacidoze kontinuiranom infuzijom brzodjelujućeg inzulina uz obilnu volumnu nadoknadu. Po poboljšanju općeg stanja i relevantnih laboratorijskih parametara, bolesnik je premješten na Zavod za endokrinologiju radi obrade i liječenja novootkrivene šećerne bolesti intenziviranom inzulinskom terapijom. Po dospijeću nalaza specifičnih autoantitijela, prati se izrazito povišen titar antitijela na dekarboksilazu glutaminske kiseline (264.6 IU/ml) te antitijela na stanice otočića gušterače (68.12 IU/ml) uz uredne vrijednosti titra antitijela na inzulin. Vrijednost glikiranog hemoglobina (HbA1c) bila je veća od 14%.

Rasprava: Dijagnoza OI zbog učestalih prijeloma, boli i smanjene pokretljivosti značajno remeti kvalitetu života. Pojedina istraživanja sugeriraju povećan rizik od metaboličkih poremećaja u bolesnika sa dijagnozom OI, uključujući šećernu bolest. Manja mišićna masa, smanjena fizička aktivnost i mogući učinci terapije kortikosteroidima pridonose razvoju inzulinske rezistencije. Šećerna bolest tipa 1 povezana je sa smanjenom mineralnom gustoćom kosti, što se pripisuje nedostatku inzulina i hiperglikemiji, koji također povećavaju rizik od prijeloma. Još uvijek ne postoje medicinski utemeljeni dokazi da bolesnici s dijagnozom OI, prvenstveno genetskog poremećaja, imaju povećan rizik od nastanka šećerne bolesti tipa 1. Aktualno je u literaturi opisan samo jedan slučaj OI

sa autoimunim dijabetesom. Neovisno o tipu šećerne bolesti, ovi rijetki slučajevi trebali bi ostvariti pravo na CGM sustave putem zdravstvenog osiguravatelja, obzirom na utjecaj istih na kvalitetu života.

Zaključak: Ovaj prikaz slučaja ukazuje na rijetku povezanost osteogenesis imperfekta i šećerne bolesti tipa 1, dviju bolesti sa izraženim negativnim učinkom na koštano tkivo. Iako ne postoje jasni medicinski dokazi o uzročno-posljedičnoj vezi između ove dvije bolesti, potrebno je obratiti pažnju na metaboličke poremećaje kod pacijenata s OI. Kombinacija ovih patologija zahtijeva posebnu skrb, uključujući i pravo na sustav kontinuiranog praćenja glukoze, kako bi se smanjio rizik od razvoja dijabetičkih komplikacija i u konačnici novih prijeloma u takvih bolesnika. Daljnja istraživanja potrebna su kako bi se bolje razumjela ova rijetka koincidencija i omogućio optimalan pristup liječenju.

Ključne riječi: dijabetička ketoacidoza; osteogenesis imperfekta; šećerna bolest, tip 1

Literatura: [1] Marmalyuk DA, Runova GE, Moshenina SE, Shapka MP, Fadeyev VV. Combination of osteogenesis imperfecta and type 1 diabetes mellitus. Diabetes mellitus. 2022;24(5):470–6.; [2] Deguchi M, Tsuji S, Katsura D, Kasahara K, Kimura F, Murakami T. Current Overview of Osteogenesis Imperfecta. Medicina (Kaunas). 2021;57(5):464.; [3] Botor M, Fus-Kujawa A, Uroczynska M, Stepien KL, Galicka A, Gawron K, et al. Osteogenesis Imperfecta: Current and Prospective Therapies. Biomolecules. 2021;11(10):1493.

S24 Challenges in quality of life with osteogenesis imperfecta – A case report of newly diagnosed autoimmune diabetes

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Introduction and objective: Osteogenesis imperfecta (OI) is a genetic connective tissue disorder caused by abnormalities in type I collagen synthesis. Clinical manifestations range from mild, almost asymptomatic forms to severe forms associated with high perinatal mortality. In addition to the fractures, course of disease can be accompanied by short stature, skeletal deformity and joint hypermobility. The occurrence of diabetes is a rare but serious comorbidity in patients with OI.

Case report: We report a case of a 61-year-old patient presented to the emergency neurology department due to a suspected stroke. Heteroanamnestically, it was found that the patient had been experiencing diffuse headaches accompanied by difficulty speaking for the past two days. Personal medical history revealed a diagnosis of OI established in childhood, with extensive limb deformities rendering the patient immobile. An urgent CT scan of the brain ruled out any acute neurological condition. Laboratory findings showed metabolic acidosis with hyperglycemia and elevated inflammatory parameters. A chest X-ray described basal left-sided pneumonia. The patient was admitted to the intensive care unit for treatment of diabetic ketoacidosis with continuous infusion of rapid-acting insulin and aggressive fluid resuscitation. Upon improvement in general condition and relevant laboratory parameters, the patient was transferred to the Department of Endocrinology for further evaluation and treatment of newly diagnosed diabetes with intensified insulin therapy. Specific autoantibody tests revealed significantly elevated titers of glutamic acid decarboxylase antibodies (264.6 IU/ml) and islet cell antibodies (68.12 IU/ml), with normal insulin autoantibody titers. Glycated hemoglobin (HbA1c) levels exceeded 14%.

Discussion: The diagnosis of OI significantly impacts the quality of life due to frequent fractures, pain, and reduced mobility. Some studies suggest an increased risk of metabolic disorders in patients with OI, including diabetes. Reduced muscle mass, decreased physical activity, and possible effects of corticosteroid therapy contribute to insulin resistance. Type 1 diabetes mellitus is associated with a decreased bone mineral density, which is mostly attributed to insulin deficiency and hyperglycemia, which also increase the risk of fractures. However, there is still no strong medical evidence that patients with OI, primarily a genetic disorder, have an increased risk of developing type 1

diabetes. So far, there has been only one case of OI with autoimmune diabetes reported in the literature. Regardless of the type of diabetes, these rare cases should be eligible for CGM systems, given their impact on quality of life.

Conclusion: This case report highlights the rare association between osteogenesis imperfecta and type 1 diabetes, two diseases with a pronounced negative effect on bone tissue. Although there is no clear medical evidence of a causal relationship between these two diseases, attention should be given to metabolic disorders in OI patients. The combination of these pathologies requires special care, including the right to a continuous glucose monitoring system, to reduce the risk of developing diabetic complications and eventually new fractures in such patients. Further research is needed to better understand this rare coincidence and optimize treatment approaches.

Key words: diabetic ketoacidosis; diabetes mellitus, type 1; osteogenesis imperfecta

Literature: [1] **Marmalyuk DA, Runova GE, Moshenina SE, Shapka MP, Fadeyev VV. Combination of osteogenesis imperfecta and type 1 diabetes mellitus. Diabetes mellitus. 2022;24(5):470–6.;** [2] **Deguchi M, Tsuji S, Katsura D, Kasahara K, Kimura F, Murakami T. Current Overview of Osteogenesis Imperfecta. Medicina (Kaunas). 2021;57(5):464.;** [3] **Botor M, Fus-Kujawa A, Uroczynska M, Stepien KL, Galicka A, Gawron K, et al. Osteogenesis Imperfecta: Current and Prospective Therapies. Biomolecules. 2021;11(10):1493.**

S25 Monogenetski tip dijabetesa; MODY — prikaz slučaja

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Uvod: Monogenetski tipovi dijabetesa rijetka su skupina dijabetesa s udjelom od 2-3 % od ukupnog broja bolesnika sa šećernom bolesti, dok je MODY (Maturity onset diabetes of young) najčešći podtip. Riječ je o nasljednim bolestima čije je (rano) prepoznavanje značajno radi pravilnoga liječenja, a time i prevenciju komplikacija šećerne bolesti.

Prikaz slučaja: Pacijentica u dobi od 25 godina bila je hospitalizirana zbog kliničke sumnje na dijabetičku ketoacidozu, a bez jasnih kriterija za istu. Nekoliko mjeseci ranije primjetila je simptome poliurije i polidipsije uz gubitak na tjelesnoj masi od ukupno 2 kilograma (ITM 19,9 kg/m2). Učinjenom laboratorijskom obradom potvrđena je negativna vrijednost protutijela karakterističnih za dijabetes tipa 1 (GAD65, ICA, IA2), međutim pacijentica je otpuštena s preporukom bazal-oral shemom terapije uz dijabetičku dijetu te CGM-uređajem. Tijekom daljnjih kontrolnih pregleda pacijentici je dodatno učinjena i proširena laboratorijska obrada kojom su vrijednosti inzulina i C-peptida dospjele značajno snižene. Uvidima u CGM-izvješća pacijentica je u kontrolnim intervalima u ciljnom rasponu (TIR) provodila većinu vremena (> 90 %) uz epizode hipoglikemije (2-3 %), stoga su doze dugodjelujućeg inzulina minimalno korigirane. S obzirom na tijek bolesti, ali i ostale anamnestičke te kliničke podatke postavljena je sumnja na monogenetski tip dijabetesa, stoga je učinjeno genetsko testiranje za najčešći podtip – MODY 3.

Rasprava: Prikazanim slučajem jasno se uočava netipičnost kliničke slike dijabetesa tipa 1 ili tipa 2, stoga je nužno razmišljati i o drugim tipovima dijabetesa. Bez obzira na to što je MODY tip dijabetesa sporoprogredirajuća bolest, u navedenom prikazu slučaja pacijentici je već prilikom započinjanja liječenja bila potrebna inzulinska terapija u više doza.

Zaključak: Unatoč značajno manjoj zastupljenosti monogenetskih tipova dijabetesa, potrebno je pravodobno posumnjati da je riječ o navedenom tipu dijabetesa kako bi se na vrijeme postavila odgovarajuća dijagnoza, a sve u svrhu odgovarajućeg liječenja, odnosno odgode nastupa kroničnih komplikacija bolesti.

Ključne riječi: MODY, monogenetski tip, inzulin

Literatura: [1] Nkonge KM, Nkonge DK, Nkonge TN. The epidemiology, molecular pathogenesis, diagnosis, and treatment of maturity-onset diabetes of the young (MODY). Clin Diabetes Endocrinol. 2020;6(1):20; [2] Urakami T. Maturity-onset diabetes of the young (MODY): current perspectives on diagnosis and treatment. Diabetes Metab Syndr Obes. 2019;12:1047-56

S25 Monogenetic type of diabetes: MODY – a case report

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Introduction: Monogenetic types of diabetes are a rare group of diabetes, accounting for 2-3% of the total number of patients with diabetes, while MODY (Maturity onset diabetes of young) is the most common subtype. These are hereditary diseases whose (early) recognition is important for proper treatment and thus for the prevention of complications of diabetes.

Case report: A 25-year-old patient was hospitalized due to clinical suspicion of diabetic ketoacidosis, without clear criteria for it. Several months earlier, she had noticed symptoms of polyuria and polydipsia with a total weight loss of 2 kilograms (BMI 19.9 kg/m2). Laboratory testing confirmed the negative value of antibodies characteristic of type 1 diabetes (GAD65, ICA, IA2), however, the patient was discharged with a recommendation for a basal-oral therapy regimen with a diabetic diet and a CGM device. During further follow-up examinations, the patient underwent additional and expanded laboratory testing, which resulted in significantly reduced insulin and C-peptide values. Insights into the CGM reports showed that the patient spent most of the time (> 90%) in the target range (TIR) during the control intervals with episodes of hypoglycemia (2-3%), therefore the doses of long-acting insulin were minimally adjusted. Given the course of the disease, as well as other anamnestic and clinical data, a monogenetic type of diabetes was suspected, therefore genetic testing for the most common subtype – MODY 3 was performed.

Discussion: The presented case clearly demonstrates the atypicality of the clinical picture of type 1 or type 2 diabetes, therefore it is necessary to consider other types of diabetes. Regardless of the fact that MODY type of diabetes is a slowly progressive disease, in the above case report the patient already required insulin therapy in multiple doses when starting treatment.

Conclusion: Despite the significantly lower prevalence of monogenetic types of diabetes, it is necessary to suspect this type of diabetes in a timely manner in order to establish an appropriate diagnosis in time, all for the purpose of appropriate treatment, i.e. delaying the onset of chronic complications of the disease.

Keywords: MODY, monogenetic type, insulin

Literature: [1] Nkonge KM, Nkonge DK, Nkonge TN. The epidemiology, molecular pathogenesis, diagnosis, and treatment of maturity-onset diabetes of the young (MODY). Clin Diabetes Endocrinol. 2020;6(1):20; [2] Urakami T. Maturity-onset diabetes of the young (MODY): current perspectives on diagnosis and treatment. Diabetes Metab Syndr Obes. 2019;12:1047-56

S26 Metode redukcije tjelesne mase

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Uvod s ciljem: Prevalencija prekomjerne tjelesne mase i debljine u Hrvatskoj predstavlja značajan javnozdravstveni problem. Prema istraživanjima, više od polovice odraslog stanovništva ima prekomjernu tjelesnu masu ili debljinu, pri čemu su muškarci više pogođeni od žena. Sličan trend primjećuje se i među djecom, što povećava rizik od kroničnih nezaraznih bolesti poput dijabetesa tipa 2, kardiovaskularnih bolesti i određenih vrsta karcinoma. Glavni uzroci uključuju nepravilnu prehranu, sjedilački način života i nedostatak tjelesne aktivnosti.

Prikaz slučaja: Prikazujemo tri različite bolesnice liječene u KBC Osijek od kojih se svaka odlučila na jednu od metoda redukcije tjelesne mase unutar godine dana praćenja. Bolesnica 1. liječena je općim mjerama te je uz redovito nutricionističko savjetovanje i pridržavanje plana prehrane unutar godine dana reducirala tjelesnu masu ukupno 40 kg (početni ITM 48,7 kg/m², nakon godine dana 31,9 kg/m², ukupno je izgubila 32,1 kg ukupnog masnog tkiva i 7,9 kg mišićnog tkiva, dok se visceralno masno tkivo smanjilo s 20 na 11). Bolesnica 2. liječena je farmakoterapijom liraglutidom te je unutar godine dana reducirala tjelesnu masu za ukupno 20 kg (početni ITM 47,6 kg/m², nakon godine dana 40,7 kg/m², ukupno je izgubila 18,8 kg ukupnog masnog tkiva i 1,2 kg mišićnog tkiva, dok se visceralno masno tkivo smanjilo s 18 na 14). Bolesnica 3. liječena je operacijskom metodom (sleeve gastrektomija) unutar godine dana reducirala je tjelesnu masu za ukupno 40 kg (početni ITM 36,1 kg/m², nakon godine dana 23,8 kg/m², ukupno izgubila 27,1 kg ukupnog masnog tkiva i 12,9 kg mišićnog tkiva, visceralno masno tkivo smanjilo se s 11 na 7).

Rasprava: Osnova liječenja debljine uključuje promjenu životnih navika, s naglaskom na pravilnu prehranu i povećanje tjelesne aktivnosti, gdje se preporuča individualiziran pristup. Opće mjere se provode kod sva tri oblika liječenja debljine. Farmakoterapija se primjenjuje kod bolesnika s indeksom tjelesne mase (ITM) ≥30 kg/m² ili ≥27 kg/m² uz prisutnost komorbiditeta poput dijabetesa tipa 2 ili hipertenzije. Lijekovi odobreni za liječenje debljine djeluju na smanjenje osjećaja gladi, povećanje potrošnje energije ili smanjenje apsorpcije masti. Najčešće korišteni lijekovi uključuju liraglutid, GLP-1 agonist odobren za liječenje debljine te tirzepatid, dugodjelujući agonist receptora za GIP i GLP-1, koji djeluju na regulaciju apetita. Barijatrijska kirurgija predstavlja opciju za bolesnike s

teškom pretilošću (ITM ≥40 kg/m² ili ≥35 kg/m² uz komorbiditete) kod kojih konzervativne metode nisu dale zadovoljavajuće rezultate. Najčešće metode uključuju gastričnu premosnicu, sleeve gastrektomiju (rukavnu resekciju želuca) i postavljanje želučane premosnice. Barijatrijska kirurgija ne samo da dovodi do značajnog gubitka tjelesne mase, već se može poboljšati ili čak izliječiti pridružene metaboličke poremećaje, poput dijabetesa tipa 2.

Zaključak: Prevencija i liječenje debljine zahtijevaju multidisciplinarni pristup, uključujući edukaciju, promicanje zdravih životnih navika te podršku zdravstvenog sustava i društva u cjelini. Bez obzira na koju se od metoda liječenja debljine bolesnici odlučili ključni su kontinuirano praćenje bolesnika i podrška stručnog tima kako bi se postigli dugoročno održivi rezultati.

Ključne riječi: debljina, redukcija tjelesne mase, farmakoterapija, barijatrijska kirurgija

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S26 Methods of body mass reduction

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Introduction and aim: The prevalence of overweight and obesity in Croatia represents a significant public health problem. According to research, more than half of the adult population is either overweight or obese, with men being more affected than women. A similar trend is observed among children, which increases the risk of chronic non-infectious diseases such as type 2 diabetes, cardiovascular diseases and certain types of cancer. The main causes include an improper diet a sedentary lifestyle and a lack of physical activity.

Case report: We present three different patients treated at KBC Osijek, each of whom opted for one of the methods of weight reduction within a year of follow-up. Patient 1 was treated with general measures and, with regular nutritional counseling and adherence to a diet plan, reduced her body weight by a total of 40 kg within a year (initial BMI 48,7 kg/m², after a year 31,9 kg/m². She lost a total of 32,1 kg of total fat tissue and 7,9 kg of muscle tissue, while visceral fat tissue decreased from 20 to 11). Patient 2 was treated with pharmacotherapy using liraglutide and reduced her body weight by a total of 20 kg within a year (initial BMI 47,6 kg/m², after a year 40,7 kg/m². She lost a total of 18,8 kg of total fat tissue and 1,2 kg of muscle tissue, while visceral fat tissue decreased from 18 to 14). Patient 3 was treated with a surgical method (sleeve gastrectomy) and within a year she reduced her body weight by a total of 40 kg (initial BMI 36.1 kg/m², after a year 23,8 kg/m², She lost a total of 27,1 kg of total fat tissue and 12,9 kg of muscle tissue, visceral fat tissue decreased from 11 to 7).

Discussion: The foundation of obesity treatment includes changing lifestyle habits, with an emphasis on proper nutrition and increasing physical activity, where an individualized approach is recommended. General measures are implemented in all three forms of obesity treatment. Pharmacotherapy is used in patients with a body mass index (BMI) ≥30 kg/m² or ≥27 kg/m² in the presence of comorbidities such as type 2 diabetes or hypertension. Drugs approved for the treatment of obesity act to reduce hunger, increase energy expenditure or reduce fat absorption. The most commonly used drugs include liraglutide, a GLP-1 agonist approved for the treatment of obesity, and tirzepatide, a long-acting GIP and GLP-1 receptor agonist, both of which act on appetite regulation. Bariatric surgery is an option for patients with severe obesity (BMI ≥40 kg/m² or ≥35 kg/m² with

comorbidities) in whom conservative methods have not yielded satisfactory results. The most common methods include gastric bypass, sleeve gastrectomy, and adjustable gastric banding. Bariatric surgery not only leads to significant weight loss, but can also improve or even cure associated metabolic disorders, such as type 2 diabetes.

Conclusion: Prevention and treatment of obesity require a multidisciplinary approach, including education, promotion of healthy lifestyle habits, and support from the health system and society as a whole. Regardless of which method of obesity treatment patients choose, continuous monitoring and support from a professional team are essential to achieving long-term sustainable results.

Keywords: obesity, body weight reduction, pharmacotherapy, bariatric surgery

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S27 Dijabetička ketoacidoza inducirana pembrolizumabom: prikaz slučaja

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Uvod s ciljem: Pembrolizumab, humanizirano monoklonsko protutijelo, sve je češće prisutuno kao imunoterapija metastatskih karcinoma gdje je pokazalo veliku učinkovitost u postizanju remisije. Međutim, do sada je već zabilježen značajan broj imunološki posredovanih nuspojava povezanih sa primjenom pembrolizumaba, uključujući endokrinopatije poput tireoiditisa, hipofizitisa te, iako rijetko, dijabetičke ketoacidoze, koja se javlja u svega 0,1 % slučajeva, ali predstavlja po život opasno stanje.

Prikaz slučaja: Prikazujemo slučaj 76-godišnjeg bolesnika hospitalizranog na Zavodu za endokrinologiju radi obrade i liječenja dijabetičke ketoacidoze. Bolesnik je bio upućen na OHBP od strane liječnika obiteljske medicine zbog povišenih vrijednosti glikemije, pojačanog žeđanja i učestalog mokrenja, gdje je pregledan putem hitne internističke ambulante u kojoj je laboratorijskom obradom verificirana dijabetička ketoacidoza. Odmah po prijemu u terapiju su uključene infuzije kristaloidnih otopina s dodatkom brzodjelujućeg inzulina na što se prati stabilizacija glikemije te korekcija elektrolitskog disbalansa. Bolesnik se od ranije prati zbog šećerne bolesti te je u aktivnom onkološkom liječenju melanoma sa sekundarizmima na mozgu. U 11. mjesecu 2022. godine hospitaliziran je na Klinici za neurologiju zbog desnostrane slabosti i učestalih padova, kada mu je učinjenom obradom potvrđen ekspanzivni proces sa sumnjom na metastaze u mozgu. Premješten je na Zavod za neurokirurgiju gdje je temeljem kliničke slike i MR nalaza indicirana operacija radi uklanjanja interkranijskog ekspanzivnog procesa lijevo frontalno. Patohistološkom analizom utvrđeno je da je navedeni ekspanzivni proces u mozgu metastaza melanoma. Bolesnik je u 1. mjesecu 2023. godine hospitaliziran na Zavodu za onkologiju radi provođena palijativne radioterapije mozga te je putem multidisciplinarnog tima indicirana sustavna terapija pembrolizumabom u 5 ciklusa koja je ponovljena 2024. godine zbog novih sekundarizama . Tijekom hospitalizacije na Zavodu za endokrinologiju učinjen je kontrolni CT mozga na kojem je opisana progresija rasta metastaze cerebeluma te je učinjena kontrola neurokirurga i onkologa. Zadovoljavajuća regulacija glikemije postiže se primjenom intenzivirane inzulinske terapije te se provodi edukacija bolesnika o primjeni inzulina.

Rasprava: Pembrolizumab se tijekom godina pokazao izuzetno uspješnim kod bolesnika sa metastazama različitih karcinoma, no kod liječenja su zabilježene brojne endokrinološke komplikacije, uključujući dijabetičku ketoacidozu. Pembrolizumab inhibira PD-1 receptor na T-limfocitima, što pojačava imunološki odgovor protiv tumorskih stanica, ali istovremeno može dovesti do autoimunog oštećenja beta-stanica gušterače. Hipofizitis, koji može uzrokovati sekundarnu adrenalnu insuficijenciju i hipotireozu, također je česta nuspojava imunoterapije. Prepoznavanje i pravodobno liječenje ovih stanja ključno je za nastavak onkološkog liječenja uz minimiziranje rizika za bolesnika.

Zaključak: Unatoč tome što je dijabetička ketoacidoza rijetka pojava kod terapije pembrolizumabom izuzetno ju je važno pravovremeno prepoznati i početi sa liječenjem. Praćenje bolesnika liječenih ovim lijekom te suradnja između endokrinologa, onkologa i drugih specijalista ključna je za adekvatno liječenje mogućih komplikacija, čime se omogućava nastavak onkološkog liječenja.

Ključne riječi: dijabetička ketoacidoza, imunoterapija, pembrolizumab

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S27 Pembrolizumab-induced diabetic ketoacidosis: a case report

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Introduction: Pembrolizumab, a humanized monoclonal antibody, is increasingly used as an immunotherapy for metastatic carcinomas, where it has demonstrated significant efficacy in achieving remission. However, a significant number of immune-mediated adverse events associated with pembrolizumab treatment have been reported to date, including endocrine disorders such as thyroiditis, hypophysitis, and, although rarely, diabetic ketoacidosis, which occurs in only 0.1% of cases but represents a life-threatening condition.

Case report: We present the case of a 76-year-old patient hospitalized at the Department of Endocrinology for the management and treatment of diabetic ketoacidosis. The patient was referred to the Hospital Emergency Department by his family physician due to elevated blood glucose levels, increased thirst, and frequent urination, where he was evaluated in the emergency internal medicine clinic and diabetic ketoacidosis was confirmed through laboratory analysis. Immediately upon admission, treatment was initiated with infusions of crystalloid solutions supplemented with rapid-acting insulin, which led to stabilization of blood glucose levels and correction of electrolyte imbalances. The patient had a history of diabetes and was under active oncological treatment for melanoma with brain metastases. In November 2022, he was hospitalized at the Neurology Clinic due to right-sided weakness and frequent falls, during which evaluation confirmed an expansive lesion suspicious for brain metastases. He was subsequently transferred to the Department of Neurosurgery, where, based on clinical presentation and MRI findings, surgery was indicated to remove the intracranial expansive lesion in the left frontal region. Pathohistological analysis confirmed that the intracranial expansive lesion was a melanoma metastasis. In January 2023, the patient was hospitalized at the Oncology Department for palliative brain radiotherapy, and a multidisciplinary team recommended systemic therapy with pembrolizumab administered in 5 cycles, which was repeated in 2024 due to new secondary lesions. During his hospitalization at the Department of Endocrinology, a follow-up CT scan of the brain was performed, which revealed progression of the cerebellar metastasis; this

prompted further consultations with a neurosurgeon and an oncologist. Satisfactory glycemic regulation was achieved through intensified insulin therapy, along with patient education on insulin administration.

Discussion: Pembrolizumab has proven to be highly successful over the years in patients with metastases from various carcinomas, yet numerous endocrine complications have been recorded during treatment, including diabetic ketoacidosis. Pembrolizumab inhibits the PD-1 receptor on T-lymphocytes, enhancing the immune response against tumor cells, but it can also lead to autoimmune damage to the pancreatic beta-cells. Hypophysitis, which may cause secondary adrenal insufficiency and hypothyroidism, is another common adverse effect of immunotherapy. Recognizing and promptly treating these conditions is crucial for the continuation of oncological therapy while minimizing risks to the patient.

Conclusion: Although diabetic ketoacidosis is a rare occurrence during pembrolizumab therapy, it is extremely important to recognize it in a timely manner and initiate treatment. Monitoring patients treated with this medication, along with collaboration among endocrinologists, oncologists, and other specialists is essential for adequately managing potential complications, thereby enabling the continuation of oncological treatment.

Keywords: diabetic ketoacidosis, immunotherapy, pembrolizumab

Literature: [1] **Doodnauth AV, Klar M, Mulatu YS, Malik ZR, Patel KH, McFarlane SI. Pembrolizumab-Induced Hypophysitis With Isolated Adrenocorticotropic Hormone (ACTH) Deficiency: A Rare Immune-Mediated Adverse Event. Cureus. 2021 Jun 5;** [2] **Chaudry A, Chaudry M, Aslam J. Pembrolizumab: An Immunotherapeutic Agent Causing Endocrinopathies. Cureus. 2020 Jun 25;** [3] **Sankar K, Macfarlane M, Cooper O, Falk J. Pembrolizumab-Induced Diabetic Ketoacidosis: A Review of Critical Care Case. Cureus. 2021 Oct 22;**

S28 Dijabetička ketoacidoza u bolesnika sa šećernom bolesti tipa 2 liječenog SGLT-2 inhibitorima u akutnom alkoholiziranom stanju

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Uvod: Dijabetička ketoacidoza je ozbiljna metabolička komplikacija šećerne bolesti koja može nastati u stanjima apsolutnog ili relativnog manjka inzulina ili prilikom upotrebe određenih lijekova. Kod bolesnika sa šećernom bolesti tipa 2 u alkoholiziranom stanju klinička slika može biti složenija zbog preklapanja s alkoholnom ketoacidozom. Alkohol potiče ketoacidozu smanjenjem sekrecije inzulina, povećanjem ketogeneze i poremećajem glukoneogeneze, često uz dehidraciju, povraćanje i gladovanje.

Prikaz slučaja: Bolenik u dobi od 42 godine, koji ranije nije teže bolovao, hospitaliziran je zbog izmjerenih visokih vrijednosti glikemije natašte (12,9 mmol/l) uz suhoću usta, pojačano žeđanje i učestalo mokrenje u trajanju od mjesec dana. Tijekom hospitalizacije učinjena je obrada novootkrivene šećerne bolesti tipa 2, vrijednost HbA1c iznosila je 11,2% uz održanu endogenu sekreciju inzulina i vrijednost C peptida 1,33 nmol/l. Mikrovaskularne komplikacije nisu utvrđene, a od makrovaskularnih komplikacija nađene su samo početne aterosklerotske promjene karotidnih arterija. Glikemija je u početku regulirana intenziviranom inzulinskom terapijom, a kasnije kombiniranom peroralnom terapijom dapagliflozinom i metforminom. Bolesnik je dobrog općerg stanja otpušten kući uz navedenu terapiju peroralnim antidijabeticima, statinima i acetilsalicilnom kiselinom. Dan nakon otpusta, bolesnik je pronađen na cesti bez svijesti te je hospitaliziran u Jedinici intenzivnog liječenja zbog euglikemijske dijabetičke i alkoholne ketoacidoze. U inicijalnim laboratorijskim nalazima izdvajaju se blaga metabolička acidoza (pH 7,22) uz ketone u krvi 3,2 mmol/l i ketonuriju te vrijednosti GUK 5,2 mmol/l i etanola 1,33 g/l. Po stabilizaciji stanja u Jedinici intenzivnog liječenja, bolesnik je premješten na Odjel za endokrinologiju gdje je glikemija ponovno regulirana intenziviranom inzulinskom terapijom, a od četvrtog dana boravka i peroralnim antidijabeticima sitagliptinom i metforminom. Prilikom otpusta, osim sitagliptina i metformina, savjetovano je i uvođenje pioglitazona ovisno o vrijednostima glikemije.

Rasprava: Ovaj slučaj ističe rizike kombinacije alkohola i SGLT-2 inhibitora koja može dovesti do ozbiljnih metaboličkih komplikacija poput euglikemijske dijabetičke i alkoholne ketoacidoze. SGLT-2 inhibitori potiču ketogenezu smanjenjem sekrecije inzulina i povećanjem glukagona, dok alkohol dodatno inhibira glukoneogenezu i izaziva dehidraciju, što zajedno povećava rizik od ketoacidoze. Također, zamjena dapagliflozina sigurnijim lijekovima, poput sitagliptina, bila je nužna za sprječavanje ponovne ketoacidoze.

Zaključak: Preklapanje alkoholne i euglikemijske dijabetičke ketoacidoze može otežavati postavljanje dijagnoze zbog normalnih vrijednosti glikemije, što naglašava važnost acidobaznog statusa te ketona u krvi i urinu kod bolesnika sa simptomima poput mučnine, povraćanja ili poremećaja svijesti. Neophodna je edukacija bolesnika o rizicima konzumacije alkohola tijekom uzimanja peroralnih antidijabetika te važnosti pravovremenog prepoznavanja metaboličkih poremećaja.

Ključne riječi: dijabetička ketoacidoza, alkohol, SGLT-2 inhibitor

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S28 Diabetic Ketoacidosis in Type 2 Diabetes Patient with Acute Alcohol Intoxication: A Case Report

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Introduction: Diabetic ketoacidosis is a severe metabolic complication of diabetes that can occur in conditions of absolute or relative insulin deficiency or with the use of certain medications. In patients with type 2 diabetes who are in an intoxicated state due to alcohol consumption, the clinical presentation may be more complicated due to the overlap with alcoholic ketoacidosis. Alcohol promotes ketoacidosis by reducing insulin secretion, increasing ketogenesis, and disrupting gluconeogenesis, often accompanied by dehydration, vomiting, and starvation.

Case report: A 42-year-old patient, previously healthy, was hospitalized due to measured high fasting blood glucose levels (12.9 mmol/l) with dry mouth, increased thirst, and frequent urination for the past month. During hospitalization, an assessment of newly diagnosed type 2 diabetes mellitus was performed, with an HbA1c value of 11.2%, preserved endogenous insulin secretion and a C-peptide value of 1.33 nmol/l. Microvascular complications were not found, and only early atherosclerotic changes in the carotid arteries were detected as macrovascular complications. Initially, blood glucose was controlled with intensified insulin therapy, and later with combined oral therapy using dapagliflozin and metformin. The patient was discharged in good general condition with oral antidiabetic therapy, statins and acetylsalicylic acid. The day after discharge, the patient was found unconscious on the street and was hospitalized in the Intensive Care Unit due to euglycemic diabetic and alcoholic ketoacidosis. Initial laboratory results showed metabolic acidosis (pH 7.22), blood ketones 3.2 mmol/l, ketonuria, blood glucose 5.2 mmol/l, and ethanol 1.33 g/l. After stabilizing the condition in the Intensive Care Unit, the patient was transferred to the Endocrinology Department, where blood glucose was again regulated with intensified insulin therapy, and from the fourth day of hospitalization with oral antidiabetic therapy including sitagliptin and metformin. Upon discharge, in addition to sitagliptin and metformin, the introduction of pioglitazone was recommended depending on blood glucose levels.

Discussion: This case highlights the risks of combining alcohol with SGLT-2 inhibitors, which can lead to serious metabolic complications such as euglycemic diabetic and alcoholic ketoacidosis. SGLT-2 inhibitors promote ketogenesis by reducing insulin secretion and increasing glucagon, while alcohol further inhibits gluconeogenesis and induces dehydration, which together increases the risk of ketoacidosis. Furthermore, replacing dapagliflozin with a safer medication, like sitagliptin, was necessary to prevent recurrent ketoacidosis.

Conclusion: The overlap of alcoholic ketoacidosis and euglycemic diabetic ketoacidosis can complicate the diagnostic process due to normal blood glucose levels, emphasizing the importance of measuring acid-base status as well as blood and urine ketones in patients with symptoms like nausea, vomiting, or altered consciousness. Patient education about the risks of alcohol consumption while taking oral antidiabetic medications and the importance of timely recognition of metabolic disturbances is essential.

Keywords: diabetic ketoacidosis, alcohol, SGLT-2 inhibitor

S29 Preciznija kontrola šećerne bolesti tipa 1 kod neverbalne djece s Downovim sindromom: uloga CGM sustava

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Uvod s ciljem: Kontinuirano praćenje glukoze (CGM, engl. Continuous glucose monitoring) predstavlja značajan napredak u regulaciji šećerne bolesti tipa 1. Ti sustavi omogućuju neprekidno mjerenje i bilježenje glikemije pružajući uvid u koncentraciju glukoze u svakom trenutku, dakle omogućuju retrogradni uvid u koncentracije glukoze tijekom dana i noći. Time se smanjuje potreba za čestim kapilarnim pregledom glikemije i omogućava brza reakcija na hipoglikemijske i hiperglikemijske epizode. Kod pacijenata s posebnim potrebama, osobito onih koji nisu verbalni, ova tehnologija značajno poboljšava kvalitetu skrbi i smanjuje rizik od akutnih komplikacija.

Prikaz slučaja: Predstavljamo slučaj pacijenta s Downovim sindromom i šećernom bolesti tipa 1, liječenog inzulinskom terapijom, s izraženim poteškoćama u regulaciji glikemije zbog nemogućnosti verbalizacije simptoma sa skrbnicima. Prije uvođenja CGM-a, uočene su velike oscilacije glikemije s čestim epizodama hipoglikemije tijekom noći i hiperglikemije tijekom dana. Vrijednosti HbA1c bile su visoke (oko 8,3 %), a jutarnji GUK (glukoza u krvi) često iznad 18 mmol/L unatoč prilagođenoj inzulinskoj terapiji. Obitelj pacijenta suočavala se s brojnim izazovima u svakodnevnoj regulaciji bolesti, uključujući potrebu za učestalim mjerenjima razine glukoze, prilagodbom doza inzulina te stalnim praćenjem pacijentovog ponašanja, govora tijela i mimike kako bi na vrijeme prepoznali moguće promjene u njegovom stanju. Ovi zahtjevi značajno su utjecali na kvalitetu života svih članova obitelji, stvarajući dodatni stres i emocionalnu opterećenost. Tijekom redovitih pregleda u sklopu obiteljske medicine primijećene su poteškoće u kontroli bolesti te učestale hospitalizacije. Uočeno je da su učestale hipoglikemije značajno narušavale kako njegovu svakodnevicu, tako i svakodnevicu njegove obitelji. U suradnji s endokrinološkim timom uveden je CGM sustav kako bi se poboljšala kontrola glukoze i smanjio rizik od akutnih komplikacija. Nakon uvođenja CGM-a, laboratorijski nalazi su se značajno poboljšali. Prosječna vrijednost glukoze iznosila je 9,0 mmol/L, TIR (vrijeme u ciljanim vrijednostima) povećano je na 66 %, a TAR (vrijeme iznad ciljnih vrijednosti) smanjeno na 34 %, uz potpuno eliminirane epizode hipoglikemije (TBR 0 %). HbA1c je smanjen na 6,5 %, a vrijednosti glukoze tijekom noći i jutarnjih sati su stabilizirane. Roditelji pacijenta sada putem mobilne aplikacije mogu u svakom trenutku pratiti razine glukoze, što im omogućava brzu intervenciju u slučaju oscilacija. Također,

pacijent više ne mora prolaziti kroz učestalo kapilarno ispitivanje glikemije, što je značajno smanjilo stres povezan s kontrolom šećerne bolesti.

Rasprava: Ovi rezultati ukazuju na važnost primjene CGM tehnologije u pacijentima s posebnim potrebama, naglašavajući potrebu za multidisciplinarnim pristupom u skrbi o složenim slučajevima.

Zaključak: Ovaj slučaj naglašava ključnu ulogu CGM sustava u poboljšanju kontrole šećerne bolesti tipa 1 kod pacijenata s mentalnom retardacijom i otežanom komunikacijom. Implementacija ove tehnologije omogućila je bolju regulaciju glikemije, smanjenje rizika od akutnih komplikacija i značajno poboljšanje kvalitete života pacijenta i njegove obitelji. Uvođenje CGM-a trebalo bi postati standard u skrbi za pacijente s posebnim potrebama i dijabetesom tip 1. Također, ovaj slučaj ističe važnost multidisciplinarnog pristupa, gdje obiteljski liječnik igra ključnu ulogu u prepoznavanju problema, koordinaciji skrbi i poboljšanju kvalitete života pacijenta i njegove obitelji.

Ključne riječi: šećerna bolest tipa 1, CGM, Downov sindrom

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S29 More Precise Control of Type 1 Diabetes in Nonverbal Children with Down Syndrome: The Role of the CGM System

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Introduction: Continuous Glucose Monitoring (CGM) represents a significant advancement in managing type 1 diabetes mellitus, providing real-time glucose levels and reducing the need for frequent capillary blood glucose checks. It also enables rapid responses to hypoglycemic and hyperglycemic episodes. In patients with intellectual disabilities—especially those who are nonverbal—this technology significantly improves the quality of care and reduces the risk of acute complications.

Case Presentation: We present the case of a patient with Down syndrome and type 1 diabetes mellitus, treated with insulin therapy, who experienced significant difficulties in regulating blood glucose due to an inability to verbalize symptoms. Prior to the introduction of CGM, large fluctuations in blood glucose were observed, with frequent episodes of nocturnal hypoglycemia and daytime hyperglycemia. HbA1c levels were high (approximately 8.3 %), and the morning blood glucose was often above 18 mmol/L despite adjusted insulin therapy. The patient's family faced numerous challenges in the daily management of the disease, including the need for frequent blood glucose measurements, adjustments in insulin dosages, and constant monitoring of the patient's behavior, body language, and facial expressions to promptly recognize possible changes in his condition. These demands significantly impacted the quality of life of all family members, creating additional stress and emotional burden. During regular check-ups with his family medicine physician, difficulties in disease control and frequent hospitalizations were noted. In collaboration with the endocrinology team, a CGM system was introduced to improve blood glucose control and reduce the risk of acute complications. After the introduction of CGM, laboratory findings improved significantly. The average blood glucose level was 9.0 mmol/L, with Time in Range (TIR) increased to 66% and Time Above Range (TAR) reduced to 34%, while hypoglycemic episodes were completely eliminated (Time Below Range, TBR, 0%). HbA1c decreased to 6.5%, and blood glucose values during the night and early morning stabilized. The patient's parents can now monitor blood glucose levels at any time via a mobile application, enabling rapid intervention in case of fluctuations. Additionally, the patient no longer has to undergo frequent capillary blood glucose tests, which has significantly reduced the stress associated with diabetes management.

Discussion: These results highlight the importance of implementing CGM technology in patients with special needs, emphasizing the need for a multidisciplinary approach in the care of complex cases.

Conclusion: This case emphasizes the key role of CGM in improving diabetes control in patients with communication challenges. Implementing this technology has allowed for better glycemic regulation, a reduction in the risk of acute complications, and a significant improvement in the quality of life for both the patient and his family. The introduction of CGM should become a standard component in the care of patients with special needs and type 1 diabetes. Furthermore, this case highlights the importance of a multidisciplinary approach, with the family medicine physician playing a crucial role in identifying issues, coordinating care, and enhancing the overall quality of life for the patient and his family.

Keywords: diabetes mellitus type 1, CGM, Down syndrome

Literature: [1] American Diabetes Association. Standards of medical care in diabetes—2024. Diabetes Care. 2024;47(Suppl 1):S1-S200. Available at: https://diabetesjournals.org/care/article/47/Supplement_1/S1/XXXXX; [2] Danne T, Nimri R, Battelino T, et al. International consensus on use of continuous glucose monitoring. Diabetes Care. 2017;40(12):1631-1640. Available at: https://diabetesjournals.org/care/article/40/12/1631/XXXXX; [3] Beck RW, Riddlesworth T, Ruedy K, et al. Continuous glucose monitoring versus usual care in patients with type 1 diabetes. JAMA. 2017;317(4):371-378. Available at: https://jamanetwork.com/journals/jama/fullarticle/XXXXX; [4] Buckingham B, Cheng P, Beck RW, et al. CGM impact on glycemic control in nonverbal pediatric patients with type 1 diabetes. Diabetes Technol Ther. 2021;23(6):385-392. Available at: https://www.liebertpub.com/doi/full/XXXXX; [5] Frier BM. Hypoglycemia in diabetes mellitus: epidemiology and clinical implications. Nat Rev Endocrinol. 2014;10(12):711-722. Available at: https://www.nature.com/articles/nrendo.2014.170

POREMEĆAJ METABOLIZMA LIPIDA I URATA

S30 Klinička inercija – neizgovorena prepreka u liječenju kardiovaskularnih bolesti – preliminarni nalazi studije EHUH-2

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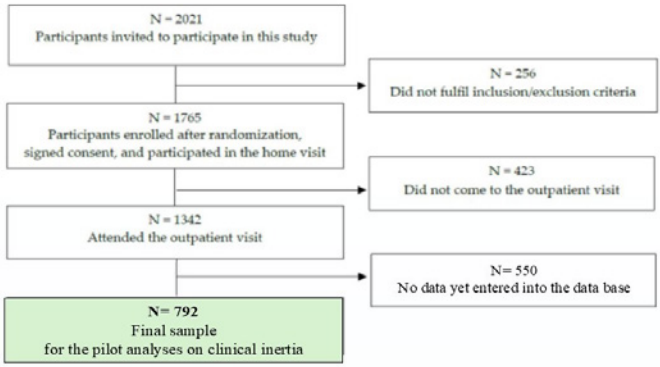
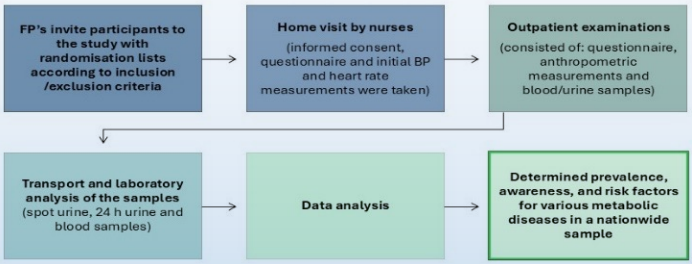
Uvod: Hipertenzija i dislipidemija glavni su kardiovaskularni čimbenici rizika koji značajno doprinose morbiditetu i mortalitetu u svijetu. Učinkovito liječenje zahtijeva pravovremenu dijagnozu i prilagodbu liječenja. Klinička inercija—neuspjeh u započinjanju ili intenzifikaciji terapije unatoč nepostizanju ciljeva liječenja—ostaje ključna prepreka koja dovodi do suboptimalne kontrole arterijskog tlaka i razine lipida.

Metode: Studija EHUH-2 (Epidemiologija hipertenzije i unosa soli u Hrvatskoj 2) najveća je nacionalna studija ove vrste na temu epidemiologije kardiovaskularnih čimbenika rizika i bolesti. U istraživanje je inicijalno pozvano 2021 sudionika, od kojih je nakon randomizacije, potpisivanja informiranog pristanka i kućnih posjeta uključeno 1705 ispitanika. Ambulantni pregled obavilo je 1342 sudionika, a u ovu preliminarnu analizu kliničke inercije uključeno je 792 ispitanika (slika ispod). Dizajn studije također je prikazan na slici.



Study design



Ova studija procjenjuje kliničku inerciju u liječenju dislipidemije i hipertenzije u Hrvatskoj. Granice LDL-C i statusa hipertenzije definirane su prema najnovijim smjernicama Europskog društva za aterosklerozu (EAS) i Europskog društva za hipertenziju (ESH).

Definicije kliničke inercije u hipertenziji:
a) Niska klinička inercija = Tri antihipertenzivna (AH) lijeka, pri čemu su dva u punoj dozi
b) Srednja klinička inercija = Tri AH lijeka, pri čemu je jedan u punoj dozi
c) Visoka klinička inercija = Nema terapije ILI jedan AH lijek ILI dva AH lijeka ILI tri AH lijeka bez tiazidnih/tiazidima sličnih diuretika ILI tri AH lijeka (uključujući tiazide), ali niti jedan lijek nije u punoj dozi

Definicije kliničke inercije u dislipidemiji:
a) Niska klinička inercija = Puna doza visokointenzivnog statina bez ezetimiba
b) Srednja klinička inercija = Polovična doza visokointenzivnog ili puna doza srednjeintenzivnog statina bez ezetimiba
c) Visoka klinička inercija = Nema terapije ILI manje od polovične doze visokointenzivnog statina bez ezetimiba

Rezultati: Ukupan broj ispitanika u ovom uzorku bio je 792. Prevalencija hipertenzije iznosila je 56% (n=442), od čega je 18,2% (n=144) imalo kontroliranu hipertenziju, 13,1% (n=104) nekontroliranu hipertenziju, dok 24,5% (n=194) nije primalo antihipertenzivnu terapiju. Od ukupno 298 slučajeva nekontrolirane hipertenzije bilo je 0 slučajeva niske i srednje inercije, 293 slučaja (99%) visoke kliničke inercije te 4 slučaja rezistentne hipertenzije. Prevalencija dislipidemije iznosila je 72%, od čega je 4,2% (n=33) imalo kontroliranu dislipidemiju, 60,4% (n=478) nije primalo terapiju, dok je 7,7% (n=61) imalo nekontroliranu dislipidemiju. Od ukupno 538 slučajeva nekontrolirane dislipidemije bila su 2 slučaja (0,4%) niske inercije, 14 slučajeva (3.6%) srednje inercije te 522 slučaja (97%) visoke kliničke inercije.

Zaključak: Klinička inercija ostaje neprepoznata prepreka u upravljanju kardiovaskularnim bolestima. Ova studija pokazala je visoku prevalenciju kliničke inercije u liječenju dislipidemije i hipertenzije u Hrvatskoj te nužnu potrebu za poboljšanjima (npr. edukacija, javnozdravstvene inicijative i bolja komunikacija liječnik-pacijent) u svakodnevnoj kliničkoj praksi.

Ključne riječi: Klinička inercija, Dislipidemija, Hipertenzija, EHUH-2 istraživanje, Kardiovaskularne bolesti

S30 Clinical Inertia – the unspoken barrier to cardiovascular disease management – preliminary EHUH-2 findings

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Introduction: Hypertension and dyslipidemia are major cardiovascular risk factors, significantly contributing to morbidity and mortality worldwide. Effective management requires timely diagnosis and treatment adjustments. Clinical inertia—the failure to initiate or escalate therapy despite unmet treatment goals—remains a critical barrier, leading to suboptimal control of blood pressure and lipid levels. This study evaluated clinical inertia in dyslipidemia and hypertension treatment in Croatia.

Methods: EHUH-2 study (Epidemiology of hypertension and salt intake in Croatia 2) is the biggest nationwide study of this type on the epidemiology of cardiovascular risk factors and diseases. 2021 Participants were invited to participate in this study. 1705 participants enrolled after randomization, signed consent and participated in home visits. 1342 participants attended the outpatient visit. 792 participants were included in this preliminary analysis of clinical inertia (image below). The study design is also shown in the image below.

Different subgroups' cut-off points for LDL-C and hypertension status were based on the most recent EAS and ESH guidelines.

Definitions for clinical inertia in hypertension:
a) Low clinical inertia = Three AH medications where only two are in full dose
b) Medium clinical inertia = Three AH medications where only one is in full dose
c) High clinical inertia = Not on treatment OR one AH medication OR two AH medications OR three AH medications without thiazide/thiazide-like diuretics OR three AH medications (including thiazides) where no AH medication is in full dose

Definitions for clinical inertia in dyslipidemia:
a) Low clinical inertia = full dose high-intensity statin without ezetimibe
b) Medium clinical inertia = half dose high-intensity or full dose medium-intensity statin without ezetimibe
c) High clinical inertia = Not on treatment OR less than half dose of a high-intensity statin without ezetimibe

Results: The total number of subjects in this data sample was 792. The prevalence of hypertension was 56% (n=442), 18.2% (n=144) had controlled hypertension, 13.1% (n=104) had uncontrolled hypertension, while 24.5% (n=194) had untreated hypertension. In the total of 298 cases of uncontrolled hypertension, there were 0 cases of low and middle inertia and 293 cases (99%) of high clinical inertia, with the other 4 cases being subjects with resistant hypertension. The prevalence of dyslipidemia was 72%, 4.2% (n=33) had controlled dyslipidemia, 60.4% (n=478) had untreated dyslipidemia and 7.7% (n=61) had uncontrolled dyslipidemia. In the total of 538 cases of uncontrolled dyslipidemia, there were 2 cases (0.4%) of low inertia, 14 cases of middle inertia (2.6%) and 522 cases (97%) of high clinical inertia.

Conclusion: Clinical inertia remains an unspoken barrier to cardiovascular disease management. This study showed a high prevalence of clinical inertia in dyslipidemia and hypertension treatment in Croatia and the urgent need for improvement (e.g. education, public health initiatives, and better patient-doctor communication) in everyday clinical work.

Keywords: Clinical inertia, Dyslipidemia, Hypertension, EHUH-2 study, Cardiovascular disease

S31 Važno je znati svoj broj – redukcija LDL kolesterola i prevencija velikog neželjenog kardiovaskularnog događaja u bolesnika s porodičnom hiperkolesterolemijom

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Uvod s ciljem: Porodična hiperkolesterolemija autosomno je dominantna nasljedna bolest koja uzrokuje povišene vrijednosti LDL kolesterola ubrzavajući razvoj ateroklerotske bolesti i povećavajući rizik ranog razvoja neželjenog kardiovaskularnog događaja.

Prikaz slučaja: Mladić u dobi od 23 godine javio se u Hitnu službu naše ustanove zbog bolova u prsištu u naporu koji su se inicijalno pojavili nekoliko sati prije prijema. U trenutku pregleda zabilježeno je da je bio pušač prekomjerne tjelesne težine koji ranije nije teže bolovao niti je uzimao kroničnu terapiju. Anamanestički podaci upućivali su na iznimno opterećenu obiteljsku povijest ranog razvoja kardiovaskularne bolesti – majka i mlađa sestra od rane mladosti su znale za visoke vrijednosti LDL kolesterola, a djed (majčin otac) je umro od posljedica srčanog udara u dobi od 27 godina. S obzirom na navedno učinjena je hitna koronarografija kojom je utvrđena značajna stenoza LAD. Iz laboratorijskih nalaza izdvajale su se visoke vrijednosti ukupnog kolesterola (13.2 mmol/L), LDL kolesterola (10.91 mmol/L) te blaže povišene vrijednosti triglicerida (1.99 mmol/L). Na temelju zbroja bodova Dutch Lipid Clinical Network-a (DLCN 11) postavljena je definitivna dijagnoza porodične hiperkolesterolemije. Bolesnik je, uz svu ostalu potrebnu terapiju, otpušten i s preporukom strogog pridržavanja redukcijsko - hipolipemične dijete i uzimanja maksimalne doze visokopotentnog statina i ezetimiba. Pridržavao se danih smjernica. Nakon 8 tjedana u kontrolnim laboratorijskim nalazima bilo je vidljivo djelomično sniženje LDL kolesterola (4.79 mmol/L). U terapiju je, s obzirom na navedeno, dodan i PCSK9i, na što se pratilo dodatno sniženje LDL kolesterola (1,36 mmol/L) i postizanje ciljnih vrijednosti. Tijekom daljnjeg praćenja bolesnik je bio dobrog općeg stanja, propisanu terapiju redovito je uzimao i dobro podnosio te se kontrolirao putem našeg Referentnog Centra. Nije došlo do razvoja novih neželjenih kardiovaskularnih događaja.

Rasprava: Obiteljska i osobna anamneza te vrijednosti kolesterola upućuju na dijagnozu porodične hiperkolesterolemije. S obzirom da se bolest nasljeđuje autosomno dominantno važno je rano prepoznati oboljele te započeti s liječenjem hipolipemicima. Zdrav način prehrane i tjelesna akitvnost mogu malim dijelom sniziti vrijednosti kolesterola, ali bez hipolipemične terapije u osoba s porodičnom hiperkolesterolemijom ciljne vrijednosti nemoguće je postići. Cijeloživotni rizik razvoja kardiovaskularne bolesti

u osoba s porodičnom hiperkolesterolemijom višestruko je veći no u općoj populaciji, ali u heterozigota se redukcijom LDL kolesterola uz pomoć hipolipemika može postići smanjenje rizika na razinu onog u općoj populaciji. Najizraženiji učinak prevencije postiže se prije razvoja prvog neželjenog događaja, a ciljne vrijednosti se snizuju ukoliko je osoba ranije imala neželjeni kardiovaksularni događaj.

Zaključak: Rano prepoznavanje osoba s porodičnom hiperkolesterolemijom, njihovo pravovremeno liječenje te postizanje ciljnih vrijednosti LDL kolesterola može spriječiti razvoj neželjenog kardiovaskularnog događaja.

Ključne riječi: porodična hiperkolesterolemija, statini, ezetimib, PCSK9 inhibitori

Reference: [1] Bouhairie VE, Goldberg AC. Familial hypercholesterolemia. Cardiol Clin. 2015 May;33(2):169-79. doi: 10.1016/j.ccl.2015.01.001. PMID: 25939291; PMCID: PMC4472364.; [2] Neil A, Cooper J, Betteridge J, et al. Reductions in all-cause, cancer, and coronary mortality in statin-treated patients with heterozygous familial hypercholesterolaemia: a prospective registry study. Eur Heart J. 2008;29:2625–2633. doi: 10.1093/eurheartj/ehn422.; [3] Duell PB, Maki KC. From the Editors: Familial hypercholesterolemia: Still underdiagnosed and undertreated. J Clin Lipidol. 2024 Mar-Apr;18(2):e130-e131. doi: 10.1016/j.jacl.2024.03.005. PMID: 38702142.

S31 It Is Important To Know Your Numbers – Reduction Of The LDL Cholesterol And Prevention Of The Major Adverse Cardiovascular Incident In Patient With Familiar Hypercholesterolemia

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Introduction and Goal: Familial hypercholesterolemia is an autosomal dominant hereditary disease that causes elevated LDL cholesterol values, accelerating the development of atherosclerotic diseases and increasing the risk of early development of major cardiovascular adverse events.

Case report: A 23-year-old young man reported to the emergency department of our institution because of chest pains during exertion that initially appeared a few hours before admission. At the time of the examination, it was noted that he was an overweight smoker who had not previously suffered from severe pain or was taking chronic therapy. The anamnestic data indicated an extremely burdensome family history of early development of cardiovascular disease - the mother and younger sister knew about high LDL cholesterol values from an early age, and the grandfather (mother´s father) died of a heart attack at the age of 27. Given the above, an emergency coronary angiography was performed, which revealed a significant stenosis of the LAD. From the laboratory findings, high values of total cholesterol (13.2 mmol/L), LDL cholesterol (10.91 mmol/L) and slightly elevated values of triglycerides (1.99 mmol/L) stood out. A definitive diagnosis of familial hypercholesterolemia was made on the basis of the Dutch Lipid Clinical Network score (DLCN 11). The patient, in addition to all other necessary therapy, was discharged with a recommendation to strictly adhere to a reduction-hypolipemic diet and take the maximum dose of a high-potency statin and ezetimibe. He followed the given guidelines. After 8 weeks, the control laboratory findings showed a partial lowering of LDL cholesterol (4.79 mmol/L). Considering the above, PCSK9i was added to the therapy, which was followed by an additional reduction of LDL cholesterol (1.36 mmol/L) and the achievement of target values. During further follow-up, the patient was in a good general condition, he regularly took the prescribed therapy and tolerated it well, and was monitored through our Reference Center. No new adverse cardiovascular events occurred.

Discussion: Family and personal history, and LDL cholesterol values can suggest a diagnosis of familial hypercholesterolemia. Given that the disease is inherited in an autosomal dominant manner, it is important to recognize patients early and start

treatment with hypolipemic drugs. A healthy diet and physical activity can lower cholesterol values to a small extent. Still, without hypolipemic therapy in people with familial hypercholesterolemia, it is impossible to reach the target values. The lifetime risk of developing cardiovascular disease in people with familial hypercholesterolemia is significantly higher than in the general population. In patients with heterozygote forme, reduction of LDL cholesterol with the help of hypolipemic agents can reduce the risk to the level of the general population. The most pronounced effect of prevention is achieved before the development of the first adverse event, and the target values are lowered if the person previously had an adverse cardiovascular event.

Conclusion: Early recognition of patients with familial hypercholesterolemia, their timely treatment, and achievement of LDL cholesterol target values can prevent the development of an unwanted cardiovascular event.

Keywords: familial hypercholesterolemia, statines, ezetimibe, PCSK9 inhibitors

Reference: [1] **Bouhairie VE, Goldberg AC. Familial hypercholesterolemia. Cardiol Clin. 2015 May;33(2):169-79. doi: 10.1016/j.ccl.2015.01.001. PMID: 25939291; PMCID: PMC4472364.;** [2] **Neil A, Cooper J, Betteridge J, et al. Reductions in all-cause, cancer, and coronary mortality in statin-treated patients with heterozygous familial hypercholesterolaemia: a prospective registry study. Eur Heart J. 2008;29:2625–2633. doi: 10.1093/eurheartj/ehn422.** [3] **Duell PB, Maki KC. From the Editors: Familial hypercholesterolemia: Still underdiagnosed and undertreated. J Clin Lipidol. 2024 Mar-Apr;18(2):e130-e131. doi: 10.1016/j.jacl.2024.03.005. PMID: 38702142.**

S32 Primarna trikuspidalna insuficijencija,fibrilacija atrija i amiodaronski tireoiditis (hipertireoza)

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Uvod s ciljem: Poznato je da hormoni štitne žlijezde djeluju na kardiovaskularni sustav. Najčešće kardijalne manifestacije hipertireoze su arterijska hipertenzija i fibrilacija atrija. Rjeđe komplikacije su srčano popuštanje te vrlo rijetko i trikuspidalna regurgitacija. Dodatno, primjena amiodarona u sklopu liječenja fibrilacije atrija može dovesti do razvoja hipertireoze te u ovom slučaju kompliciratiliječenje trikuspidalne insuficijencije.
Prikaz slučaja: Bolesnica u dobi od 63 godine hospitalizirana je u Klinici za bolesti srca i krvnih žila KBC Sestre Milosrdnice radi sinkronizirane elektrokardioverzije simptomatske perzistentne fibrilacije atrija. Kod bolesnice se ranije u nekoliko navrata odustalo od planirane elektrokardioverzije zbog tromba u lijevom atriju prikazanog transezofagijskom ehokardiografijom. U ovom boravku je isključeno postojanje tromba u lijevom atriju te je učinjena sinkronizirana elektrokardioverzija čime je postignut stabilan sinusni ritam. Učinjen je kontrolni ultrazvuk srca kojim je prikazan dilatiran desni ventrikul uz tešku trikuspidalnu insuficijenciju zbog čega je učinjena i daljna obrada te su isključeni svi potencijalni sekundarni uzroci trikuspidalne insuficijencije uključujući Ebsteinovu anomaliju, atrijski septalni defekt, karcinoid, plućnu emboliju te hipertireozu. Vrijednosti TSH, fT3, fT4 su bile uredne. Kod bolesnice je zaključeno da se radi o primarnoj bolesti trikuspidalnog zaliska, predviđen je operativni zahvat te je u terapiju zbog kontrole srčanog ritma uveden amiodaron. Preoperativno su ponovno određeni hormoni štitne žlijezde. S obzirom na izrazito snižene vrijednosti TSH uz povišene anti-TPO, anti-TG i antitijela na TSH receptor zaključeno je da se radi o amiodaronskom tireoiditisu tipa 1 te je u terapiju uveden tireostatik tiamazol. Dodatno je učinjen ultrazvuk štitnjače kojim se u srednjem dijelu lijevog režnja prikazan inhomogeni čvor s hipoehogenim rubom i kalcifikatima veličine 19x14x15 cm. Scintigrafija štitnjače je prikazala izo- do hipofunkcionalni čvor koji izbočuje medijalnu konturu srednje trećine lijevog režnja. Uz primjenu tireostatske terapije došlo je do normalizacije vrijednosti hormona štitne žlijezde (TSH 2,3 mIU) te je prekinuto liječenje tireostatikom. Daljnji tijek liječenja se zakomplicirao perforacijom divertikula crijeva zbog čega je bolesnica operirana prije predviđene operacije valvule i tireoidektomije. Postoperativno je zabilježen suprimiran TSH te je u terapiju ponovno uveden tireostatik.

Rasprava: U ovom slučaju prikazali smo bolesnicu s inicijalno utvrđenom primarnom trikuspidalnom insuficijencijom kod koje se uz liječenje amiodaronom razvila hipertireoza. Kod bolesnice povišene vrijednosti antitijela na TSH receptore upućuju na amiodaronski tireoiditis tipa 1 uz ultrazvučno opisan čvor koji je na scintigrafiji

hipofunkcionalan. Uz uvedenu tireostatsku terapiju postignuta je normalizacija vrijednosti hormona štitne žlijezde. Nakon hitne operacije perforiranog divertikula crijeva ponovno su zabilježene suprimirane vrijednosti TSH zbog čega je u terapiju ponovno uveden tireostatik uz napomenu da je sada bolesnica bez amiodarona u terapiji što potvrđuje Gravesovu hipertireozu.

Zaključak: Usprkos činjenici da hipertireoza može biti u podlozi srčanog popuštanja, fibrilacije atrija i trikuspidalne insuficijencije u ovom slučaju se hipertireoza razvila nakon upotrebe amiodarona što govori u prilog amiodaronskom tireoiditisu tipa 1 uz hipofunkcionalni čvor lijevog režnja štitnjače. Liječenje hipertireoze odgodilo je operaciju trikuspidalnog zaliska. Daljnji tijek bolesti kompliciran je perforacijom divertikula. Po oporavku od operacije crijeva slijedi kontrola kardiologa uz praćenje po endokrinologu te dogovor oko strategije liječenja valvularne bolesti i bolesti štitnjače. Prikazom ove bolesnice htjeli smo prikazati koliko može biti kompleksna dijagnostika i liječenje određenih bolesti uz potencijalne brojne komplikacije.

Ključne riječi: trikuspidalna insuficijencija, amidaronski tireoiditis, fibrilacija atrija, čvor u štitnjači

S32 Primary tricuspid regurgitation, atrial fibrillation and amiodarone thyroiditis (hyperthyroidism)

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Introduction with aim: Thyroid hormones are known to affect the cardiovascular system. The most common cardiac manifestations of hyperthyroidism are arterial hypertension and atrial fibrillation. Less common complications include heart failure and, in rare instances, tricuspid regurgitation. Furthermore, amiodarone, a medication used to treat atrial fibrillation, can induce hyperthyroidism, potentially complicating the management of tricuspid regurgitation as seeninthiscase.

Case report: A 63-year-old patient wasadmitted to the Department of Cardiovascular Diseasesat the Sestremilosrdnice University Hospital Centerfor synchronized electrocardioversion of symptomatic persistent atrial fibrillation. In this patient, previously planned electrocardioversionswere repeatedly abandoneddue to the presence of a left atrial thrombus detected on transesophageal echocardiography. During this stay, the existence of a thrombus in the left atrium was ruled out, and a synchronized electrocardioversion was performed, which achieved a stable sinus rhythm.Control echocardiographyshowed a dilated right ventricle with severe tricuspid regurgitation.During the subsequent follow-up, potential secondary causes of tricuspid regurgitation, including Ebstein´s anomaly, atrial septal defect, carcinoid syndrome, pulmonary embolism, and hyperthyroidism, were ruled out.TSH, fT3, fT4 values were normal. Consequently, it was concluded that this was a case of primary disease of the tricuspid valveand an operation was planned. Amiodarone was added to the treatment regimen for rhythm control. Preoperatively, thyroid function tests were repeated.Given the extremely low TSH values in the presence of elevated anti-TPO, anti-TG and TSH receptor antibodies, a diagnosis of amiodaroneinduced type 1 thyroiditis was made. Thiamazole, a thyrostaticdrug, was subsequently initiated.In addition, an ultrasound of the thyroid gland was performed, which showed an inhomogeneous nodule with a hypoechoic edge and calcifications measuring 19x14x15 cm in the middle part of the left lobe. Thyroid scintigraphy showed an iso- to hypofunctional nodule protruding from the medial contour of the middle third of the left lobe. With the use of thyrostatic therapy, the thyroid hormone value was normalized (TSH 2.3 mIU) and the thyrostatic treatment was discontinued. The clinical course was complicated by the development of a perforated colonic diverticulum, needing urgent surgical intervention prior to the planned valve replacement and thyroidectomy. Postoperatively, an suppressed TSH value was recorded. Thyrostatic therapy was resumed.

Discussion: In this case, we presented a patient with an initial diagnosis of primary tricuspid regurgitation who developed hyperthyroidism after treatment with amiodarone. In this patient, elevated values of TSH receptor antibodies suggestedamiodarone induced type 1 thyroiditis. Ultrasound revealed a nodule, which was demonstrated to be hypofunctional on scintigraphy. Initiation of thyrostatic therapy resulted in normalization of thyroid hormone levels. Following emergency surgery for perforated colonic diverticule, suppressed TSH levels wereagain detected. Thyrostatic therapy was resumed. Notably, the patient was then managed without amiodarone, confirming a diagnosis of Graves´ hyperthyroidism.

Conclussion: Despite the fact that hyperthyroidism can contribute to heart failure, atrial fibrillation and tricuspid regurgitation, in this case, hyperthyroidism occurred following the initiation of amiodarone for heart rhythm control,suggesting amiodarone induced type 1 thyroiditis with a hypofunctioning node of the left thyroid lobe. Treatment of hyperthyroidism delayed tricuspid valve surgery. The clinical course was complicated by colonic diverticuleperforation. Following recovery from bowel surgery, the patient was managed collaboratively by a cardiologist and endocrinologist to determine the optimal treatment strategy for valvular disease and thyroid dysfunction. By presenting this patient, we wanted to show how complex diagnosis and treatment of certain diseases can be, with potential numerous complications.

Key words: tricuspid regurgitation, amidarone induced thyroiditis, atrial fibrillation, thyroid nodule

S33 Hipotireoza i srce — prikaz slučaja

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Uvod: Hipotireoza je stanje smanjenog lučenja hormona štitnjače koji može biti posljedica poremećaja u štitnoj žlijezdi (primarna hipotireoza), nedovoljnog stvaranja tireotropina (engl. Thyroid Stimulating Hormon - TSH) u hipofizi (sekundarna hipotireoza) ili tireotropin-oslabađajućeg hormona (engl. Thyrotropin Releasing Hormon - TRH) u hipotalamusu (tercijarna hipotireoza). Kliničke manifestacije hipotireoze razlikuju se ovisno o težini i trajanju nedostatka hormona i očituju se na različitim organskim sustavima, a miksedemska koma najozbiljniji je oblik bolesti. U većine pacijenata hipotireoza je trajno stanje koje zahtijeva doživotno liječenje. Terapija se sastoji od nadoknade hormona štitnjače osim ako se radi o prolaznoj i/ili reverzibilnoj hipotireozi. Prikaz slučaja: 44-godišnji bolesnik s anamnezom perzistentne eritrociturije i otoskleroze koji je mjesec dana uoči hospitalizacije na Zavodu za endokrinologiju i dijabetologiju osjećao opću slabost i promuklost, a također je primijetio i podbuhlost lica uz smetnje vida desnog oka. Ambulantnim oftalmološkim pregledom utvrđen je gubitak fovealnog refleksa zahvaćenoga oka uz odignuće prema papili optičkog živca. Zbog navedenog započeta je terapija acetazolamidom i protuupalnim oftalmicima, a na kontrolnom oftalmološkom pregledu postavljena je dijagnoza centralne serozne retinopatije uz preporuku započinjanja terapije eplerenonom u početnoj dozi od 25 mg. Iz kliničkog statusa ističe se postojanje periorbitalnih edema uz auskultacijski mukle srčane tonove i elektrokardiografski zabilježenu sinus bradikardiju, frekvencije 57/min, s mikrovoltažom u standardnim odvodima. U tijeku daljnje obrade navedenih simptoma učinjena je analiza hormona štitnjače s vrijednostima TSH > 100.000 mIU/L, fT3 < 0,5 pmol/L, fT4 1,5 pmol/L i anti-TPO 29,3 IU/ml. Ultrazvučno je opisana lako nehomogenija štitnjača bez čvorova ili patoloških limfnih čvorova. Po isključenju adrenalne insuficijencije, uvedena je supstitucijska terapija levotiroksinom u dozi 1,6 mcg /kg. Biokemijskom analizom krvi nije bilo zabilježenih elektrolitnih odstupanja, ali je utvrđena hiperkolesterolemija (kolesterol 7,4 mmol/L ; LDL-kolesterol 4,7 mmol/L) uz nedostatak 25-OH vitamina D (47,1 nmol/L) i folne kiseline (7,8 nmol/L). Pacijentu je za vrijeme hospitalizacije učinjena kardiološka obrada koja je uključivala ehokardiografiju srca s potvrđenom dilatacijskom kardiomiopatijom uz reduciranu sistoličku funkciju (2D LVEF 43 %) i globalno reduciran LV GLS -12 % te dijastolička disfunkcija II. stupnja. Nije bilo verificiranih indirektnih znakova povećanih tlakova u plućnoj cirkulaciji. 24h EKG po Holteru opisan je sinusni ritam kao temeljni, prosječne frekvencije ~ 62/min (min.39/min). Zbog od ranije poznate mikrohematurije učinjena je nefrološka reevaluacija kojom se potvrdila kronična bubrežna bolest G2A3 uz vršne vrijednosti serumskog kreatinina do 142 µmol/L i proteinurije 437 mg/dU, a s obzirom na uredne nalaze prethodne obrade hematurije, proveden je imunološki probir s neupadljivim rezultatima. Pacijentu je, po otpustu iz bolnice, savjetovano genetsko testiranje na poremećaj iz spektra Alportovog

sindroma. Rana izvješća sugerirala su moguću povezanost između Alportovog sindroma i tireoiditisa, iako su to osporili Lambert i sur (1). Teška hipotireoza poznati je čimbenik koji doprinosi razvoju i napredovanju zatajenja srca (ZS), što opravdava rutinsko testiranje funkcije štitnjače kod bolesnika sa simptomima povezanim sa ZS (2). Što se tiče koegzistencije disfunkcije lijeve klijetke i Alportovog sindroma, iako je ovaj sindrom povezan s različitim srčanim abnormalnostima—posebno valvularnom zahvaćenošću—primarne kardiomiopatije rijetko su prijavljene.

Zaključak: u ovom prikazu slučaja cilj nam je naglasiti važnost pravovremenog prepoznavanja kliničkih manifestacija hipotireoze i adekvatnog uvođenja optimalne supstitucijske hormonalne terapije koja može spriječiti ozbiljne komplikacije i poboljšati ishod pacijenata.

Ključne riječi: hipotireoza, dilatacijska kardiomiopatija, Alportov sindrom, centralna serozna retinopatija

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S33 Hypothyroidism and the heart – case report

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Introduction: Hypothyroidism is a condition of reduced thyroid hormone secretion that can be the result of a disorder in the thyroid gland (primary hypothyroidism), insufficient production of thyrotropin (Thyroid Stimulating Hormone - TSH) in the pituitary gland (secondary hypothyroidism) or thyrotropin-releasing hormone (TRH) in the hypothalamus (tertiary hypothyroidism). Clinical manifestations of hypothyroidism differ depending on the severity and duration of hormone deficiency and are manifested in different organ systems. Myxedema coma is the most serious form of the disease. In most patients, hypothyroidism is a permanent condition that requires lifelong treatment. Therapy consists of thyroid hormone replacement unless it is transient and/or reversible hypothyroidism.

Case report: a 44-year-old patient with a history of persistent erythrocyturia and otosclerosis who felt general weakness and hoarseness a month prior to hospitalization at the Department of Endocrinology and Diabetology, also noticed puffiness of the face along with visual disturbances in the right eye. The ambulatory ophthalmological examination revealed the loss of the foveal reflex of the affected eye with a protrusion towards the papilla of the optic nerve. Based on these findings, therapy with acetazolamide and anti-inflammatory ophthalmic drugs was initiated. At the follow-up ophthalmological examination, a diagnosis of central serous retinopathy was established with a recommendation to initiate therapy with eplerenone at an initial dose of 25 mg. The clinical examination revealed periorbital edema, muffled heart sounds on auscultation and electrocardiographically recorded sinus bradycardia (57/min) with microvoltage in the standard leads. As a part of the further evaluation of these symptoms, thyroid hormone analysis was performed revealing TSH > 100,000 mIU/L, fT3 < 0.5 pmol/L, fT4 1.5 pmol/L and anti-TPO 29.3 IU/ml. Ultrasound described a slightly more inhomogeneous thyroid without nodules or pathological lymph nodes. After ruling out adrenal insufficiency, levothyroxine replacement therapy was started at a dose of 1.6 mcg/kg. Biochemical blood analysis revealed no electrolyte abnormalities but showed hypercholesterolemia (cholesterol 7.4 mmol/L; LDL cholesterol 4.7 mmol/L) along with deficiencies in 25-OH vitamin D (47.1 nmol/L) and folic acid (7.8 nmol/L). During hospitalization, the patient underwent a cardiac evaluation including echocardiography, which confirmed dilated cardiomyopathy with reduced systolic function (2D LVEF 43%), globally reduced LV GLS (-12%), and grade 2 diastolic dysfunction. There were no verified indirect signs of increased pressures in the pulmonary circulation. 24h Holter ECG described sinus rhythm as fundamental, average frequency ~ 62/min (min.39/min). Due to previously known microhematuria, a nephrological reevaluation was conducted, confirming chronic kidney disease G2A3 with peak serum creatinine levels of up to 142

µmol/L and proteinuria of 437 mg/dU. Given the unremarkable findings from previous hematuria evaluations, immunological screening was performed, yielding no significant abnormalities. Upon discharge, the patient was advised to undergo genetic testing for a potential Alport syndrome spectrum disorder. Early reports suggested a possible association between Alport syndrome and thyroiditis, though this has been challenged by Lambert et al (1). Severe hypothyroidism is a well-established contributor to heart failure (HF) development and progression, justifying routine thyroid function screening in patients presenting with HF-related symptoms (2). Regarding the coexistence of left ventricular dysfunction and Alport syndrome, while this syndrome has been linked to various cardiac abnormalities—particularly valvular involvement—primary cardiomyopathies were rarely reported.

Conclusion: This case report highlights the importance of the timely recognition of hypothyroidism´s clinical manifestations and the prompt initiation of optimal hormone replacement therapy which can prevent serious complications and significantly improve patient outcomes.

Key words: hypothyroidism, dilated cardiomyopathy, Alport's syndrome, central serous retinopathy

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S34 Važnost pravovremene dijagnoze MEN2A sindroma

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Uvod s ciljem: Multipla endokrina neoplazija tip 2A (MEN2A) je autosomno dominantni poremećaj s rizikom za razvoj medularnog karcinoma štitnjače, feokromocitoma te primarnog hiperparatireoidizma. Većina bolesnika s MEN2A sindromom razvije medularni karcinom štitnjače u mlađoj životnoj dobi. Cilj ovog sažetka je naglasiti važnost testiranja na MEN2 sindrom kod mlađih osoba s dijagnosticiranim medularnim karcinomom štitnjače, pogotovo kod pozitivne obiteljske anamneze.

Prikaz slučaja: Radi se 33-godišnjoj bolesnici kojoj je u 11.mj.2023.g., zbog povremenih epizoda povišenih vrijednosti krvnog tlaka unazad nekoliko godina, započeta obrada sekundarnog uzroka arterijske hipertenzije. U isto vrijeme bolesnica je pregledana od strane specijaliste nuklearne medicine zbog povišenih vrijednosti kalcitonina i suspektnog nalaza ultrazvuka štitnjače i vrata. Obrada je započeta nakon što je njezinoj majci dijagnosticiran medularni karcinom. Citološkom punkcijom potvrđen je medularni karcinom štitnjače s metastazama u limfne čvorove vrata zbog čega je upućena na žurni operativni zahvat. U 12.mj.2023.g. učinjena je totalna tireoidektomija sa selektivnom disekcijom vrata. Tijek hospitalizacije se zakomplicirao razvojem hipertenzivne krize. U tada pristiglim nalazima ranije započete obrade zabilježene su povišene vrijednosti metanefrina i normetanefrina u 24 satnom uzorku urina. Učinjen je CT abdomena na kojem su nađene dvije ekspanzivne tvorbe u desnoj nadbubrežnoj žlijezdi te jedna u lijevoj, otvorene etiologije. Bolesnica je premještena na Odjel endokrinologije gdje je učinjena dodatna endokrinološka obrada zbog sumnje na MEN2 sindrom. Obradom je isključen primarni hiperparatireoidizam, a učinjeni MR hipofize nije opisao značajnije abnormalnosti. Genetsko testiranje na RET protoonkogen je pristiglo pozitivno. U 2.mj.2024.g., uz adekvatnu preoperativnu pripremu, učinjena je desnostrana adrenalektomija i parcijalna resekcija lijeve nadbubrežne žlijezde. Patohistološki nalaz je potvrdio dijagnozu feokromocitoma. Bolesnica je postoperativno pod redovitom kontrolom endokrinologa te je dodatno od strane onkologa provedena adjuvatna radioterapija zbog metastaza medularnog karcinoma. Dobila je upute oko važnosti genetskog testiranja na MEN2 sindrom kod njenih srodnika u prvom koljenu.
Rasprava: Kod bolesnice s naknadno dokazanim MEN2A sindromom prvotno je učinjena totalna tireoidektomija s ciljem liječenja medularnog karcinoma štitnjače usprkos činjenici da se na osnovu pozitivne obiteljske anamneze na medularni karcinom te epizoda arterijske hipertenzije trebalo posumnjati na feokromocitom u sklopu ranije spomenutog sindroma. Kod bolesnika s MEN2A sindromom, ukoliko se preoperativno postavi dijagnoza feokromocitoma, indicirano je učiniti adrenalektomiju

prije tireoidektomije ili bilo koje druge operacije s ciljem izbjegavanja intraoperativne kateholaminske krize (1). Prije operacije feokromocitoma potrebno je provesti adekvatnu preoperativnu pripremu koja uključuje uvođenje blokatora alfa-receptora kroz odgovarajući vremenski period prije uvođenja blokatora beta-receptora jer u suprotnom može doći do precipitiranja hipertenzivne krize (2).

Zaključak: Ovaj prikaz slučaja ukazuje na ulogu pravovremene dijagnoze MEN2A sindroma u prevenciji razvoja potencijalnih komplikacija. Adekvatna preoperativna priprema i postoperativno praćenje, uključujući genetsko savjetovanje bliskih srodnika, predstavljaju temelj uspješnog liječenja.

Ključne riječi: multipla endokrina neoplazija, medularni karcinom štitnjače, feokromocitom

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S34 The importance of timely diagnosis of MEN2A syndrome

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Introduction with aim: Multiple Endocrine Neoplasia type 2A (MEN2A) is an autosomal dominant disorder characterized by the risk of developing medullary thyroid cancer, pheochromocytoma, and primary hyperparathyroidism. Medullary thyroid cancer is the most prevalent manifestation of MEN2A, with a high incidence typically observed in early adulthood. The aim of this summary is to emphasize the importance of testing for MEN2 syndrome in younger people with medullary cancer, especially in those with a positive family history.

Case report: In November 2023, a 33-year-old patient with a history of intermittent elevated blood pressure for several years underwent a nephrological evaluation. A workup to investigate secondary causes of hypertension was initiated. Concurrently, the patient was also evaluated by a nuclear medicine specialist due to an elevated calcitonin level and concerning thyroid and neck ultrasound findings. The workup was initiated following her mother´s diagnosis of medullary thyroid cancer. Fine-needle aspiration confirmed medullary thyroid carcinoma with neck lymph node metastases, prompting urgent surgical intervention. In December 2023, the patient underwent a total thyroidectomy with selective neck dissection. The postoperative course was complicated by a hypertensive crisis. Results from the previously initiated hypertension workup, received at that time, revealed elevated levels of metanephrine and normetanephrine in the 24-hour urine sample. A CT scan of the abdomen revealed two expansive formations of undetermined etiology within the right adrenal gland and one within the left. Due to suspicion of MEN2 syndrome, the patient was transferred to the Department of Endocrinology for further evaluation. Primary hyperthyroidism was ruled out and a pituitary MRI was performed which showed no significant abnormalities. Genetic testing for the RET proto-oncogene was positive. In February 2024, following appropriate preoperative evaluation, the patient underwent a right adrenalectomy and partial left adrenalectomy. Histopathological examination confirmed the diagnosis of pheochromocytoma. Postoperatively, the patient received routine endocrine follow-up. Due to the medullary carcinoma metastases, adjuvant radiotherapy was administered by an oncologist.The patient was counseled regarding the recommendation for first-degree relatives to undergo genetic testing for MEN2 syndrome.

Discussion: In a patient subsequently diagnosed with MEN2A syndrome, a total thyroidectomy was initially performed for the treatment of medullary thyroid cancer.

However, the patient´s positive family history of medullary thyroid cancer and history of hypertensive episodes should have prompted earlier consideration of pheochromocytoma, a component of the previously mentioned syndrome. In patients with MEN2 syndrome, if a preoperative diagnosis of pheochromocytoma is made, adrenalectomy is indicated prior to thyroidectomy or any other surgery to prevent intraoperative catecholamine crisis (1). Prior to pheochromocytoma surgery, appropriate preoperative preparation is essential. This includes alpha-receptor blockade for a sufficient period before the initiation of beta-receptor blockade, as failure to do so may precipitate a hypertensive crisis (2).

Conlusion: This clinical case indicates the role of timely diagnosis of MEN2A syndrome in the prevention of unwanted complications. Adequate preoperative regimen and postoperative follow-up, including genetic counseling of family members, are the basis of successful treatment.

Key words: multiple endocrine neoplasia, medullary thryoid carcinoma, pheochromocytoma

Literature: [1] **Marini F, Falchetti A, Del Monte F, Carbonell Sala S, Tognarini I, Luzi E, Brandi ML. Multiple endocrine neoplasia type 2. Orphanet J RareDis. 2006 Nov 14;1:45. doi: 10.1186/1750-1172-1-45. PMID: 17105651; PMCID: PMC1654141.;** [2] **Kamath AS, Singh K. Perioperative Management of Pheochromocytoma. [Updated 2023 Jul 6]. In: StatPearls [Internet]. Treasure Island (FL): StatPearlsPublishing; 2025 Jan-. Availablefrom: https://www.ncbi.nlm.nih.gov/books/NBK589634/**