

Reverzibilna demencija kod pelagre

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Sažetak

Uvod. Celijakija je oboljenje koje nastaje kao posledica određene nasledne predispozicije, trajna nepodnošljivost glutena, belančevine pšenice, ječma, raži i ovs. Prve promene kod predisponiranih događaju se na sluzokoži početnog dela tankog creva. Pri tome se smanjuje apsorpcija i javlja se nutritivni deficit. Smanjuje se unos niacina ili triptofana, što je jedan od uzroka nastanka pelagre. Pelagru karakterišu dermatitis, dijareja i demencija. Ukoliko se ne leči, javljaju se dezorijentacija, konfuzija, delirijum i, na kraju, nastupa smrt.

Prikaz slučaja. Pacijentkinja starosti 33 godine, zaposlena u fabrici obuće, majka dvoje dece, dolazi u pratnji majke. Majka primetila da je postala nezainteresovana, zaboravna, neraspoložena, ćutljiva, bez inicijative. Od malena boluje od celijakne bolesti i godinama koristi kukuruzni hleb. Od pre mesec dana ima promene na koži i prolive. Razlog dolaska - uplašila se jer juče nije znala kako da se vrati kući posle posla. Shvaćena je kao pelagroidna demencija celijaknog porekla zbog nedostatka vitamina B (B_1 , B_2 , B_3 , B_6 , B_{12}). Nakon intenzivne vitaminske terapije i adekvatne ishrane, preporučene od strane nutricioniste, poremećaj se povukao.

Zaključak. Anamneza sa tipičnom slikom je dovoljna da se posumnja na pelagru. Ukoliko znamo da je celijakija razlog uzimanja kukuruznog brašna (u kukuruznom brašnu nema vitamina B) i pojave proliva, pretpostavljamo da je to predispozicija za nastanak pelagre. Nakon dijagnostikovanja celijakije, u lečenje se moraju uključiti gastroenterolog i nutricionista. Ako se pojave komplikacije bolesti, uključuju se dermatovenerolog, infektolog, neurolog i psihijatar.

Ključne reči. Demencija, pelagra, celijakija, vitamini grupe B, osnovna zdravstvena zaštita.

Pellagra associated reversible dementia

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Abstract

Introduction: Celiac disease is a consequence of certain hereditary predisposition resulting in permanent gluten intolerance. Gluten is a protein found in wheat, barley, rye, and oats. First lesions appear in the mucosa of the proximal part of the small intestine. This leads to the decreased absorption of nutrients and consequential nutrition deficit. Niacin and tryptophan absorption is decreased which is one of the reasons for pellagra occurrence. The symptoms of pellagra are dermatitis, diarrhea, and dementia. If not treated it may cause disorientation, confusion, delirium, and ultimately death.

Case report: Female patient, 33, works in a shoe factory, mother of two, presents with her mother. Her mother noticed she has become disinterested, forgetful, moody, silent with no initiative. She suffers from celiac disease since childhood and she's been using cornbread for years. Since a month ago she started noticing skin lesions and frequent diarrheas. The main reason for her visit is that she got very scared the day before because she couldn't remember how to find her way home. Due to her basic condition, she was diagnosed with pellagra induced dementia, due to the B vitamin deficiency (B_1 , B_2 , B_3 , B_6 , B_{12}). Followed by an intensive vitamin therapy and adequate nutrition, recommended by a nutritionist, dementia symptoms withdrew.

Conclusion: A patient's history with a typical clinical presentation is good enough to suspect pellagra. Knowing that celiac disease is the reason the patient was using cornbread (which lacks vitamin B) and at the same time, the patient was experiencing diarrheas are good enough reasons to suspect pellagra. The treatment of celiac disease should include consultations of a gastroenterologist and nutritionist. Should there be any other disease complications a dermatologist, infectologist, neurologist, and psychiatrist should be consulted.

Keywords: Dementia, pellagra, celiac disease, B vitamins, Primary health care

Uvod

Celijačna bolest ili gluten senzitivna enteropatija je trajna nepodnošljivost glutena, belančevine pšenice, ječma i raži¹. Celijakija je najčešća intolerancija na hranu. Kod genetski predisponiranih osoba, imuni sistem, reagujući na uneseni gluten, dovodi do oštećenja sluznice tankog creva. Važni faktori za povećan broj obolelih od celijakije su promene u načinu ishrane, rane infekcije koje zahvataju digestivni trakt, posebno rotavirus infekcije, povećan broj porođaja carskim rezom².

Celijakija je multifaktorijska autoimuna bolest koja je genetski determinisana. Okidači bolesti su gluten i slične supstance koje se nalaze u žitaricama. Postoji različit stepen oštećenja sluznice tankog creva i različit spektar kliničkih simptoma, ali su svi posledica malapsorpcije. U pitanju je hronična bolest koja se ispoljava kod osoba koje imaju naslednu predispoziciju za ovu bolest. U populaciji je zastupljena 1%.

Najčešće manifestacije celijakije su bol ili nelagodnost u trbuhu, učestalo crevno pražnjenje, gubitak na telesnoj masi, osteoporoza, anemija, opšta slabost i iscrpljenost³. Stolica su brojne, masne, obilne i zaudarajuće. Relativno često se uočavaju i promene na koži (herpetiformni dermatitis), neurološke tegobe, kao što su mišićna slabost, poremećaj u hodu i konvulzije, različite vrste krvarenja usled nedovoljne apsorpcije vitamina K iz digestivnog trakta. Komplikacije celijakije su različite, od poremećaja stvaranja koštanog tkiva, anemije, maligne bolesti, koje se uglavnom javljaju u digestivnom traktu, pa sve do kognitivnih i mentalnih poremećaja^{3,4,5}.

Prve promene se dešavaju na crevnim resicama. Pod dejstvom glutena resice se smanjuju, dok potpuno ne nestanu. To izaziva teško oštećenje sluzokože i lošu apsorpciju hranljivih materija i vitamina. Njihova obnova se neće dogoditi dok se gluten unosi hranom.

Pelagra je oboljenje prouzrokovano nedostatkom vitamina B₃ (niacin), koji je potreban svim živim ćelijama jer ulazi u sastav mnogih enzima, te ima mnogobrojne uloge u organizmu³. Između ostalog, predstavlja neophodan faktor za normalan metabolizam nervnih ćelija⁴. Vremenom su lekari uvideli da ne obolevaju svi koji u ishrani koriste kukuruz i zaključili da je za nastanak pelagre bitan nikotin-amid, ali i izmenjena bakterijska flora u crevnom traktu. Danas je poznato da se veliki broj vitamina sintetiše u crevima pod dejstvom bakterijske flore (tiamin, riboflavin, biotin, nikotin-amid). Klinička slika pelagre se svodi na demenciju, dermatitis, dijareju.

Demencija se kod pelagre javlja pod slikom globalnog oštećenja psihičkih funkcija, pri čemu dominiraju poremećaj pamćenja, gubitak sposobnosti za vremensku i prostornu orijentaciju, poremećaj sna, apsolutna afektivna indiferentnost⁶. Demencija predstavlja pad sposobnosti pamćenja i mišljenja dovoljnog stepena da narušava aktivnosti svakodnevnog

Introduction

Celiac disease or gluten-sensitive enteropathy is precipitated by permanent intolerance of gluten, a protein found in wheat, barley, and rye¹. Celiac disease is an example of the most common food intolerance. The immune system, in genetically predisposed persons, reacts to gluten intake and leads to damage in the small intestine mucosa. An ever-growing number of celiac disease patients is allotted to changes in food habits, early infections affecting digestive tract (especially rotavirus infections), an increased number of caesarian deliveries.²

Celiac disease is a multifactorial, genetically determined, autoimmune disease. The disease trigger is gluten and similar substances found in grains. There is a varying degree of small intestine mucosa damage and a spectrum of clinical symptoms, but all of them are due to malabsorption. It's a chronic disease found in persons with a genetic predisposition. Its incidence is 1%.

The most common manifestations of the disease are abdominal pain and unease, frequent stool elimination, weight loss, osteoporosis, anemia, general weakness, and exhaustion.² The stools are frequent, fatty, excessive, and foul-smelling. Quite often the disease may cause skin eruptions (dermatitis herpetiformis), neurological symptoms, such as muscle weakness, walking disorders, and seizures, different forms of bleeding due to vitamin K malabsorption in the intestines. Celiac disease manifestations vary from osteogenesis disorders, anemia, malignant diseases (mainly of the digestive tract) to cognitive and mental disorders.^{3,4,5}

The first problems appear in the intestine villi. Due to the gluten effect, the villi shrink until they totally disappear. It leads to severe mucosa damage and malabsorption of nutrients and vitamins. Their regeneration won't occur unless gluten intake is discontinued.

Pellagra is a disease caused by a lack of vitamin B₃ (niacin), essential for all living cells because it is the part of many enzymes and it has many roles in organism functioning.³ It is an essential factor for the normal metabolism of nerve cells.⁴ Over time, doctors noticed that not all cornbread eating patients suffered from pellagra, so they concluded the lack of nicotinamide was the cause of the disease, as well as the change in intestinal bacterial flora. It's a well known fact, a great number of vitamins are synthesized in the intestines under the influence of gut bacteria (thiamine, riboflavin, biotin, nicotinamide). Clinical presentation of pellagra comes down to dementia, dermatitis, diarrhea.

Pellagra associated dementia presents with global psychological function damage, dominated by memory disorders, disorientation in time and place, sleep disorders, absolute affective indifference.⁶ Dementia is a decline in the ability to memorize and think, to a degree in which it impairs everyday functioning (doing laundry, putting clothes

života, kao što su pranje, odevanje, ishrana, lična higijena. Da bi se postavila dijagnoza demencije, navedeni simptomi i oštećenja treba da budu prisutni najmanje šest meseci.

Mogu se javiti i depresija, delirantna stanja, halucinacije ukoliko se bolest ne leči⁵. Prvi znak da se sa bolesnikom nešto dešava je kada uvidi da ne može da prati i učestvuje u razgovoru sa više ljudi. To znači da je oštećen proces prijema informacija. Lice koje ima kognitivna oštećenja ne može da se organizuje, gubi vremensku i prostornu orijentaciju, zaboravlja, ne može da upamti nove događaje, ne razume ispričani vic, ne poseduje logično razmišljanje i zaključivanje.

U krvi obolele osobe povišene su vrednosti antitigliadin-skih antitela, antitela na tkivnu transglutaminazu, endomizijum i retikulin. Dijagnoza se postavlja biopsijom sluzokože tankog creva i serološkim testovima (antitela). Od značaja su hematološke analize, imunološke analize, odnos elektrolita i radiografsko snimanje digestivnog trakta barijumom.

Ukoliko pacijent ima postavljenu dijagnozu celijačne bolesti, da ne bi došlo do pojave pelagre, tj. deficita vitamina, neophodno je da se ovakvi pacijenti obučavaju da se pridržavaju uputstva o ishrani, da ne koriste ishranu s glutenom i da doživotno redovno konzumiraju vitamine.

Prikaz slučaja

Pacijentkinja stara 33 godine, zaposlena u fabrici obuće, majka dvoje dece, dolazi po prvi put kod psihijatra u pratnji majke.

Glavni razlog dolaska je što prethodnog dana nije znala sama da se vrati kući s posla. Inače, svakog dana ide sa komšinicom do posla i vraća se s njom kući, ali je komšinica juče izašla pre vremena s posla.

Heteroanamnestički podaci: majka primetila da je poslednjih mesec dana postala zaboravna, odsutna, nezainteresovana, ćutljiva, bez inicijative, neraspoložena. Postepeno se njeno stanje pogoršavalo. Pojavilo joj se simetrično crvenilo na rukama, licu, svrbe je a počinju da se pojavljuju i plikovi. Promene na koži objašnjava činjenicom da radi u fabrici obuće i da je alergična na lepak, kožu, prljavštinu, rastvarače, boje i dr. Pre mesec dana pojavili su se i obilni prolivi, vodenasti, neprijatnog mirisa. Slabog je apetita, smršala je preko 6 kg. Žalila se da je pokvarila stomak.

Lična anamneza. Od malena boluje od celijačne bolesti, jede isključivo kukuruzni hleb, ne odlazi na redovne kontrole kod interniste, ne seća se kad je poslednji put uradila laboratorijske i biohemijske analize, nije nikad bila kod nutricioniste.

Glavni simptomi. Žali se na malaksalost, zamor, mučnine, bol u stomaku, zaboravost, ne prepoznaje poznata mesta, ne razume kad joj neko nešto kaže, povremeno je kao izgubljena. Pored toga, ima promene na koži kao i prolive.

Somatski nalaz: mršava, dehidrirana, jezik gladak, crven, na otkrivenim delovima tela, na šakama, podlakticama,

on and off, eating, personal hygiene). To diagnose dementia above mentioned symptoms should be present for at least six months.

Depression, delirium, and hallucinations may occur if the disease has not been treated.⁵ One of the first signs of trouble is when the doctor notices the patient is unable to participate in a conversation with several other persons. This implies the information reception process is being damaged. Persons with cognitive damage are unable to organize, lose time and space orientation, forget things, can not memorize new events, can not understand a joke, do not own the ability of logical thinking and conclusion making.

The blood levels of antigliadin, tissue transglutaminase, endomysium, and reticulin antibodies in the diseased persons are elevated. To confirm the diagnosis of the celiac disease, small intestine biopsy and serological tests (antibodies) should be performed. Hematologic and serological analyses are of importance, levels of electrolytes, and barium X-ray of the gastrointestinal tract.

If the patient has already been diagnosed with celiac disease, in order to prevent pellagra/vitamin deficiency, he should be advised about the change in his nutritional habits (avoid gluten containing foods and use vitamin supplements all their lives).

Case report

Female patient, 33, works in a shoe factory, mother of two, presents with her mother for her first psychiatric appointment.

Her chief complaint was that she couldn't remember how to get back home from work, on her own, the previous day. She usually goes to and from work with her neighbor, but the neighbor had to leave work earlier that day...

Heteroanamnesic data: Her mother noticed that she has become forgetful, absent, disinterested, silent, with no initiative, moody, since last month. Her condition deteriorated gradually. She noticed itchy red patches on her face, hands, and blisters started appearing as well. She considers skin lesions consequence of her working environment (works in a shoe factory, possible allergy to glue, leather, dirt, solvents, colors,...). For a month she has been suffering from excessive diarrheas, which are watery and foul-smelling. She has no appetite and lost over six kilos. She complained of an upset stomach.

Personal history. She has been suffering from celiac disease since childhood, eats only cornbread, doesn't make regular appointments with her internist, doesn't remember when she did her lab tests, and she never consulted a nutritionist.

Chief complaints. Malaise, fatigue, sickness, stomach-ache, forgetfulness, doesn't recognize known places, doesn't understand what she's being told, feels lost sometimes. Besides, she's got skin lesions and suffers from diarrhea.

vratu, simetrične kožne promene, epiderm delimično deskvamiran, na eritematoznoj podlozi vezikulobulozne promene.

Neurološki status: prisutan diskretan tremor ispruženih prstiju. Rombergov znak pozitivan, hod na širokoj osnovi. Neurolog je uradio i lumbalnu punkciju pod sumnjom na encefalitis. Likvor je bio sterilan.

Psihički status: svesna, verbalni kontakt se uspostavlja ali ne produbljuje, dezorijentisana u vremenu, nesigurna u prostoru. Izjavljuje da nije sigurna gde se nalazi i da ne bi znala da se sama vrati kući. Mišljenje konkretno, kognitivno-anamnestičke funkcije oštećene, intelektualni kapaciteti sniženi. Pamćenje oštećeno i za nove i za stare događaje. Očigledan pad voljno-nagonskih dinamizama, psihomotorna usporenost, pad koncentracije, nemogućnost računanja, logičnog zaključivanja. Socijalno povlačenje i apatija.

Psihološko testiranje: MMSE ispod 15.

Laboratorijske analize: SE 35, Le 10,22; Er 2,5; Hemoglobin 87, glukoza 7,5, urea 6,0, kreatinin 78, Fe 3,5. Rađena je koprokultura tri dana zaredom, stolice su bile bez patogenih bakterija.

Kompjuterska tomografija - CT endokranijuma je preporučena, ali nije urađena zbog kvara skenera.

Diferencijalno-dijagnostički: ovakva slika javlja se kod hroničnog alkoholizma, kod siromašnih ljudi koji isključivo konzumiraju samo kukuruz, kod Hartnupove bolesti (nasledno oboljenje), kod karcinoidnih tumora, ciroze jetre, šećerne bolesti, celijakije, hipotireoidizma, hiperkalcemije, deficita vitamina B₁₂, neurosifilisa, subduralnog hematoma.

Zbog izraženog kognitivnog oštećenja i poremećaja ponašanja, traženo je mišljenje socijalne radnice iz fabrike gde je bolesnica zaposlena. Ona je dala podatak da je pacijentkinja počela da se menja poslednjih par godina nakon što je suprug napustio porodicu. U početku su mislili da je depresivna, slali su je na bolovanja i rekreacije, ali pošto nije došlo do poboljšanja, nije više mogla da se uklopi, nije imala brzinu, koncentraciju, pravila je greške. Pakovala je obuću, ali i tu se nije snašla.

U poslednje vreme bila je upadljivog držanja i ponašanja, apatična, usporena, zbunjena, bez higijenskih navika.

Na osnovu kliničke slike, anamnestičkih podataka, laboratorijskih analiza, oboljenje je shvaćeno kao pelargoidna demencija (F02.8, E52 uzrok) u sklopu celijakije, pa je data odgovarajuća terapija.

Potvrđivanje dijagnoze laboratorijskim analizama: nizak nivo triptofana, nizak nivo niacina, kao i nizak nivo piridona u urinu. Konsultovan je internista koji je propisao terapiju.

General status: skinny, dehydrated, tongue smooth, red; simetrical skin lesions on the exposed parts of the skin (palms, forearms, neck) in the form of partly desquamated epidermis and vesiculobullose lesions on the erythematous base.

Neurological status: discret tremor of the outstretched fingers, positive Romberg test, wide-based gait. A neurologist performed a lumbar puncture, suspecting encephalitis, but CSF was sterile.

Psychological status: conscious, verbal communication possible, but not in depth; disoriented in time, unsure in space orientation. She says she's not quite sure where she's at and wouldn't be able to find her way home on her own. Thinking concrete, cognitive-amnestic functions impaired, intellectual capacity lowered. Impaired memory for new and old events. Obvious fall in voluntary-instinctive dynamisms, psychomotor slowing, decline in concentration, inability to calculate, and make a logical deduction. Social retreat and apathy.

Psychological testing: MMSE below 15.

Lab results: ESR 35, WBC 10.22, RBC 2.5, Hgb 87, glucose 7.5, BUN 6.0, creatinine 78, Fe (s) 3.5. Three consecutive coprocultures were without pathological bacteria.

CT of the head was planned, but wasn't performed due to the technical problems.

Differential diagnosis: chronic alcoholism, poor people who only consume corn, Hartnup disease (hereditary disease), carcinoid tumor, hepatic cirrhosis, diabetes mellitus, celiac disease, hypothyroidism, hypocalcemia, vitamin B₁₂ deficiency, neurosyphilis, subdural hematoma.

Due to excessive cognitive decline and mood disorder, we asked for the opinion of the social worker (from the factory the patient was working at). The social worker said she noticed the changes in the patient in the last few years, especially since her husband left the family. In the beginning, they thought she was depressed and she was sent on sick leave and recreational retreats, but she couldn't keep pace, she was slow, started losing concentration, often made mistakes. She was assigned to pack shoes into boxes, but she failed at it as well.

Lately, she has been showing conspicuous behavior, she was apathetic, slow, confused, neglected.

Based on the clinical presentation, history, and lab results we diagnosed pellagra induced dementia in celiac disease (F02.8, E52 – cause) and give adequate therapy.

The diagnosis was confirmed with additional lab findings: low level of tryptophan, niacin, and pyridone in the urine. An internist was consulted and he prescribed adequate therapy.

Terapija

Pošto je pacijentkinja bila dehidrirana, imala problem u usnoj duplji, bolno žvakanje hrane, imala učestale prolive, propisano je da dva puta dnevno prima infuziju, nedelju dana.:

1. Hartmanov rastvor 500 ml 2x1 iv.
2. amp. vit B₃ 200 mg 2x1 iv
3. amp vit B1 200 mg 2x1 iv
4. amp. vit. C 0,5g 2x1 iv
5. amp. vit B₆ 50 mg 2x1 i.v.
6. amp. OHB₁₂ na drugi dan im.

Preventivno je preporučeno:

1. Potpuno i doživotno isključenje iz ishrane namirnica koje sadrže gluten (čak i male količine glutena prave promene na čupicama i one ne mogu da se oporave).
2. Ukoliko se koristi kukuruzno brašno u ishrani, obavezno dodati belančevine životinjskog porekla, meso, mleko, jaja,

Nakon nedelju dana, objektivno stanje se poboljšalo, pacijentkinja je počela da jede, upala sluznice u ustima i jezika se povukla, stolica se regulisala tako da je mogla da uzima terapiju *per os*. Jedino je OHB₁₂ primala i.m. mesečno.

Uz odgovarajuću dijetu, polivitaminsku terapiju svi klinički znaci su se povukli za mesec dana.

Zaključak

Pelagra je potencijalno smrtonosno oboljenje, koje se odlikuje promenama na koži, gubitkom umnih sposobnosti i probavnim smetnjama. Od pelagre obolevaju žitelji siromašnih seoskih područja i to onih gde je glavna namirnica kukuruz. Pelagra je klinički sindrom koji se javlja kao posledica nedostatka niacina (faktor PP ili vit. B₃). Oboljenje nastaje isključivo ako je nedovoljan unos esencijalne aminokiseline triptofana, koja u organizmu obezbeđuje građu za sintezu niacina. Nažalost, iako se uspešno sprečava i leči pravilnom ishranom (belančevine životinjskog porekla, mleko, meso i dr, pelagra i danas odnosi veliki broj žrtava u svetu.

Preventivne mere sastoje se i u prosvetljavanju stanovništva u pogledu pravilne ishrane. Ukoliko se koristi hleb od kukuruznog brašna, u ishranu uvesti meso, odnosno belančevine životinjskog porekla, sveže voće i povrće.

Lečenje vitaminima mora biti redovno da ne bi došlo do mentalnih problema sa kliničkom slikom demencije.

Lečenje celijakije je, pre svega, izmenom načina ishrane i eliminacijom glutena. Dijeta bez glutena se doživotno sprovodi i veoma utiče na kvalitet života. Teško je pronaći hranu koja je potpuno bez glutena, a kod nekih pacijenata ova dijeta ne pokazuje povoljan efekat.

Therapy

Due to the patient's dehydration, sore mouth, painful chewing, frequent diarrheas, she was prescribed a round of infusions, twice daily, for 7 days:

1. Hartmann's solution, 0.5l 2x1 i.v.
2. Vit. B₃ amp. 200mg 2x1 i.v.
3. Vit. B₁ amp. 200mg 2x1 i.v.
4. Vit. C amp. 0.5g 2x1 i.v.
5. Vit. B₆ amp. 50mg 2x1 i.v.
6. OHB₁₂, amp. every second day i.m.

The patient was advised to:

1. Completely discontinue food containing gluten for life (even small amounts of gluten cause damage on intestinal villi and they can not recover).
2. If only cornflour is being used, animal-based proteins should be added (meat, milk, eggs).

After a week of therapy her condition improved, the patient started eating, the inflammation of the mouth mucosa and tongue declined, the stool improved and she was able to continue to take food through her mouth. She continued receiving OHB₁₂ amp. once a month i.m.

With an appropriate diet and multivitamin supplementation, she achieved full recovery in a month.

Conclusion

Pellagra is a potentially deadly disease, and it often includes symptoms such as skin lesions, mental disorders, and indigestion. It is often found in people living in the poor, rural areas, especially in those who mainly use corn. Pellagra is a clinical syndrome appearing due to the lack of niacin (PP vitamin or B₃ vitamin). It occurs only if the intake of essential amino acid tryptophan is insufficient. Tryptophan is necessary for niacin synthesis. Unfortunately, even though it's easy to prevent and treat with proper nutrition (animal-based proteins - milk, meat..) it still takes away a lot of lives worldwide.

Preventive measures include, among other things, people's education on healthy nutrition. If cornbread is being used, then animal-based proteins should be included, along with fresh fruits and vegetables.

Vitamin supplementation should be regular in order to avoid mental problems.

The most important thing in the treatment of celiac disease is to eat properly and exclude gluten. A gluten-free diet is lifelong and it affects the quality of life tremendously. It's very difficult to find the foods which are completely gluten-free and in some patients this diet is not very favorable.

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