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PARCIJALNI DIJABETES INSIPIDUS: KOMPLEKSNOST U DIFERENCIJALNOJ DIJAGNOZI

Muškarac star 43 godine je hospitalizovan u Klinici za endokrinologiju, dijabetes i bolesti metabolizma UKCS u aprilu 2024. godine zbog poliurijsko-polidipsičnog sindroma.

Na prijemu navodi da poslednja dva meseca unosi veće količine tečnosti, a poslednjih mesec dana i mokri učestalo. Ima pojačan osećaj žeđi tokom dana i noći. Noću mokri 5–8 puta u zavisnosti od unosa tečnosti. Tokom jednodnevnog merenja u kućnim uslovima popio je 5500mL, a izmokrio 7.250mL. Ambulantno je uradio MR selarne regije, kojim se verifikuje descenzija supraselarne cisterne u selarnu jamu (dif dg parcijalna "empty sella"), adenohipofiza CC dijametra 3mm, lako nehomogene strukture, bez jasne diferencijacije fokalnih zona. Ne diferencira se fiziološki hipersignal neurohipofize, stalk je odgovarajućeg položaja i dijametra. Samostalno je odradio i biohemijske analize: zadovoljavajuća glikoregulacija (glc 5.06, HbA1c 5.97%), urea 5.4, Cr 105, uredni elektroliti (Na 142.6, K 4.36), osmolalnost seruma 294mOsmol/kg, osmolalnost urina 378mOsmol/kg, specifična težina urina 1015. Navodi da ima hipertenziju poslednje tri godine. Na terapiji Norvasc tbl 5mg pritisak je adekvatno regulisan. U porodičnoj anamnezi navodi da je majka imala karcinom larinksa, koji su imali i njeni srodnici, a otac metastatski karcinom nepoznatoga primarnog porekla, sestra se leči zbog anemije.

Pacijent je na prijemu u dobrom opštem stanju, eupnoičan, acijanotičan, afebrilan. Koža i vidljive sluznice normalno prebojene, bez znakova hemoragijskog sindroma i bez periferne limfadenopatije. Metodom konfrontacije širina vidnog polja bez ispada. Nalaz nad srcem i plućima uredan; TA 120/80mmHg, fr 72/min, bez ortostaze. Abdomen b.o.

Laboratorijske analize: u KKS je verifikovana patološka leukocitarna formula, neutropenija sa limfocitozom i blaga normocitna anemija uz normalne trombocite (visoki ukupni leukociti za stepen neutropenije; Le 9.3 10^9/L, Ne 0.5 10^9/L, Ly 3.6 10^9/L , Hgb 111g/L, MCV 98 fL, Tr 253 10^9/L), normalan CRP (1.6 mg/L), zadovoljavajuća retrogradna glikoregulacija (glc 5.7mmol/l, HbA1c 5.5%), bla-

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ga hiperkreatinemija (Cr 109 umol/L), uz normalnu ureu (urea 4.7 mmol/L), bez elektrolitnog disbalansa (Na 140 mmol/L, K 4.3 mmol/L, Cl 104 mmol/L, Ca 2.42 mmol/L, PO4 1.30 mmol/L, Mg 0.91 mmol/L), granične vrednosti ALT (ALT 43 U/L), uz normalne vrednosti ostalih parametara hepatograma, povišena LDH (663 U/L). Od dodatnih analiza uzeti su ACE i hitotriozidaza, koji su normalnih vrednosti. Uzet je bazni hormonski status, koji je kompletno uredan (TSH 1.94 mIU/L, fT4 14.2 pmol/L, fT3 5.03 pmol/L, negativna organ specifična antitela, FSH 6.0 IU/L, LH 2.5 IU/L, uk. testosteron 14.13 nmol/L, SHBG 23.8 nmol/L, PRL 202 mIU/L, ACTH 3.9 pmol/L, kortizol 373 nmol//L, IGF-1 158.6 ng/mL). Sproveden je test žeđanja tokom kog osmolalnost seruma sa 298 raste do 305 mOsmol/kg uz serumski Na do 149 mmol/L, dok osmolalnost urina raste sa 482 do 528 mOsmol/kg. Po davanju DDAVP osmolalnost urina raste do 683 mOsmol/kg, ali iz tehničkih razloga nisu prikupljena još dva uzorka kako je po protokolu planirano.

Na osnovu kliničke prezentacije, rezultata testa i MR hipofize, na kom nedostaje "bright spot" neurohipofize, što ukazuje na nedostatak antidiuretskog hormona u sekretornim granulama, postavljena je dijagnoza parcijalnog dijabetesa insipidusa i u terapiju je uveden dezmopresin u dozi od 100mcg uveče (1/2 tablete).

Zbog nalaza krvne slike konsultovan je hematolog, a zbog nalaza perifernog razmaza, gde je dobijeno 16% blasta i 38% ćelija monocitne loze, pacijent je hitno preveden u Kliniku za hematologiju UKCS, gde je postavljena dijagnoza akutne mijeloidne leukemije sa neuroleukemijom. Otpočeto je specifično onkološko lečenje, koje je praćeno komplikacijama u vidu aplazije, koštane srži i apsergiloze pluća. Konačno je u septembru 2024.godine, nakon pretrage Međunarodnog registra nađen donor i učinjena je nesrodna alogena transplantacija MĆH koja je protekla bez komplikacija. Prethodno je sprovedeno terapijsko zračenje CNS-a (kraniospinalnog aksisa) u sklopu pretransplantacionog protokola. Kontrolni mijelogram ukazuje na kompletnu remisiju.

Diskusija

Diabetes insipidus (DI) je poremećaj koji karakteriše velika diureza (>3L/24h) hipoosmolalnog urina (<300mOsm/kg). U fiziološkim uslovima, ukoliko osmolalnost padne ispod 280 mOsm/kg, sekrecija vazopresina je suprimovana, što dovodi do izlučivanja hipoosmolalnog urina (<100 mOsm/kg). Kod zdravih osoba, nivo osmolalnosti, pri kome dolazi do maksimalne antidiureze (295mOsm/kg), je u isto vreme i prag žeđi. Kada osmolalnost plazme pređe ovaj prag dolazi do sekrecije vazopresina uz maksimalnu koncentraciju urina u meduli bubrega.

Postoje centralni diabetes insipidus (nastaje zbog smanjene sinteze antidiuretskog hormona; 80% arginin vazopresin sekretujućih nerona mora biti oštećeno da bi došlo do nastanka DI) i nefrogeni DI (nastaje zbog bubrežne rezistencije na cirkulišući ADH).

Zbog čestog mešanja Diabetesa insipidusa i Diabetesa mellitusa 2022. godine je na predlog velikog broja evropskih i svetskih udruženja endokrinologa, a uz podršku pacijenata, došlo do promene terminologije, te je centralni DI preimenovan u "Deficit arginin vazopresina (AVP-D)", a nefrogeni DI u "Arginin vazopresin rezistencija (AVP-R)".

Centralni diabetes insipidus je redak endokrini poremećaj koji pogađa gotovo 1 na 25.000 ljudi, ili oko 0,004% opšte populacije. Javlja se jednako kod oba pola, može se razviti u bilo kom uzrastu, pri čemu se nasledni oblici javljaju ranije u životu.

Antidiuretski hormon (ADH, arginin vazopresin (AVP)) je nonapeptid koji se kao preprohormon (prepropressophysin) prvenstveno sintetiše u supraoptičkim, a u manjoj meri i u paraventrikularnim jedrima hipotalamusa. Zatim se putem aksona transportuje do neurohipofize, gde se skladišti u sekretornim granulama, odakle se otpušta u sistemsku cirkulaciju. Pre sekrecije, preprohormon se enzimski razlaže na neurofizin i kopeptin, koji su biološki inertni, i aktivni hormon AVP. Navedene komponente se otpuštaju u plazmu u ekvimolarnim koncentracijama.

Osnovna uloga ADH je održavanje osmotske ravnoteže. Hiperosmolarna stanja najjače podstiču izlučivanje ADH. U prednjem delu hipotalamusa smešteni su osmoreceptori koji su osetljivi na promene osmolaliteta krvi. ADH svoj osnovni efekat ostvaruje na nivou bubrega, tako što se vezuje za V2 receptore u distalnim i sabirnim kanalićima, čime se pokreće intraćelijska fosforilacijska kaskada, što rezultira fosforilacijom akvaporina-2 i reapsorpcijom vode u bubregu. Do povećanog stvaranja ADH dovodi i hipovolemija. Baroreceptori u levoj pretkomori, karotidnoj arteriji i aortnom luku detektuju volumen arterijske krvi i putem n. vagusa direktno stimulišu izlučivanje ADH, koji se vezuje za V1 receptore na glatkim mišićima krvnih sudova i pokreće fosforilaciju. Ukupni efekat ove signalne kaskade je kontrakcija glatkih mišića krvnih sudova, što dovodi do povećanja ukupnog perifernog otpora i time povećanja krvnog pritiska.

Urođeni i stečeni činioci koji mogu da dovedu do centralnog diabetes insipidusa (Tabela 1)

UROĐENI	▪ Autozomno dominantno - mutacija u AVP genu ▪ Autozomno recesivno – Wolframov sindrom (mutacija WFS1 gena)
STEČENI	▪ Idiopatski – 50% ▪ Trauma – operacija hipofize, povrede, zračenje ▪ Primarni tumori – kraniofaringeom, maningeom, germinom, Cista Ratkeovog špaga, adenom hipofize, astrocitom ▪ Metastatski tumori – limfomi, leukemije, karcinom dojke, karcinom pluća ▪ Inflamatorni/autoimuni – limfocitni hipofizitis, hipofizitis udružen sa IgG4 ▪ Vaskularni – hemoragije, Sheehan's sindrom ▪ Infektivni – meningitis, encephalitis, HIV, tuberkuloza, toxoplazmoza ▪ Granulomatozna oboljenja – sarkoidoza, histiocitoza ▪ Ostalo – disfunkcija osmoreceptora, hidrocefalus, lekovi/toksini

Oko 50% bolesnika sa centralnim DI ima idiopatsku formu. Mnogi od ovih pacijenata mogu imati autoimunu destrukciju neurohipofize kao najverovatniji uzrok centralnog DI.

Trauma ili hirurški tretman neurohipofize praćeni su pojavom DI nakon 1–4 dana. Bolest može biti trajna ili dolazi do oporavka koji je definitivni ili tranzitoran; u drugom slučaju oporavak traje nekoliko dana i završava se permanentnim DI. Ovakav trifazni obrazac u dinamici sekrecije vazopresina je karakterističan za traumatski DI.

Metastaze u hipofizi predstavljaju retke komplikacije uznapredovale maligne bolesti. Još 1857. godine obdukcijom je identifikovan prvi slučaj metastatskog melanoma u hipofizu. Zatim je 1913. godine Cushing objavio ovaj jedinstven fenomen kao uzrok insipidnog dijabetesa. Hipofizne metastaze su retke i čine 1% svih operisanih tumora hipofize i <1% svih intrakranijalnih metastatskih lezija. Većina slučajeva je asimptomatska i otkrije se slučajno prilikom obdukcije ili kod pacijenata u terminalnoj fazi maligne bolesti. Kod 20–30% pacijenata sa hipofiznim metastazama je to prva manifestacija maligne bolesti. Svaki tip karcinoma može da metastazira u hipofizu. Kod žena je to najčešće rak dojke (50%), a kod muškaraca karcinom pluća (46%). Diabetes insipidus se javlja kod 50% pacijenata sa pituitarnim metastazama. Metastatsko širenje u zadnji režanj hipofize i infundibulum je posledica hematogenog širenja preko donje hipofizne arterije. Pacijenti sa pituitarnim metastazama imaju lošu prognozu i većina umire unutar 12 meseci od postavljanja dijagnoze.

Centralni dijabetes insipidus (CDI) je retka prijavljena komplikacija akutne mijeloidne leukemije (AML), javlja se u manje od 0.6%, slučajeva AML. Početak CDI tipično prethodi dijagnozi AML za 1–2 meseca. Međutim, CDI se može javiti u vreme dijagnoze AML ili kao početna manifestacija relapsa AML. Pretpostavlja se da CDI povezan sa AML predstavlja nepovoljan prognostički indikator AML, čak i kada se simptomi CDI ublažavaju primenom dezmopresina (DDAVP). Smatra se da mehanizam uključuje leukemijsku infiltraciju hipofize, što se ne vidi uvek na MRI. U jednoj studiji, čak 61,4% pacijenata sa CDI usled AML nije imalo promene na MRI, a na obdukciji 46% pacijenata sa AML imalo je perihipofizalnu leukemijsku infiltraciju u odsustvu očiglednog CDI. U poslednje vreme brojne serije slučajeva su ukazale na citogenetske aberacije hromozoma 3 i 7 kod pacijenata sa AML udruženom sa CDI. Obe aberacije rezultiraju prekomernom ekspresijom ektopične virusne integracije 1 (EVI-1). Pretpostavlja se da prekomerna ekspresija ovog gena ometa hipotalamusnu sekreciju ADH ili dovodi do njegove inaktivacije. DI može nastati zbog infiltracije, infarkta, infekcije, krvarenja ili tromboze hipofize. U studiji CDI povezanog sa AML, Ladigan je sa saradnicima analizirao 51 slučaj odraslih sa mijeloidnim malignitetima i pridruženim CDI. Prosečna starost pacijenata je 48 godina, dok je prosečna starost svih pacijenata sa AML 65 godina. AML udružen

sa CDI je češći u ženskoj populaciji (59% žena) u poređenju sa blagom prevagom muškaraca u svim AML. Većina (45/51) ovih slučajeva je *de novo* otkrivena AML, pri čemu pacijenti nemaju odranije poznatu primarnu neoplazmu koštane srži. Preostali slučajevi se sastoje od mijelodisplastičnog sindroma (MDS), koji je uobičajeni prekursor AML-a, ili od AML transformisane od aplastične anemije, MDS-a ili hronične mijelomonocitne leukemije (CMML).

Primarni simptomi zajednički za AVP-D i AVP-R uključuju polidipsiju, poliuriju i nokturiju. Poliurija se definiše kao izlučivanje urina veće od 3L dnevno. Urin je obično najviše koncentrovan ujutru zbog nedostatka unosa tečnosti tokom noći i povećane sekrecije AVP-a tokom kasnog perioda spavanja. Kao rezultat toga, prvi znak blagog do umerenog gubitka sposobnosti koncentracije urina često je nokturija. Međutim, nokturija je često nespecifična i može biti sekundarna zbog drugih faktora. Kod pacijenata sa tumorima centralnog nervnog sistema (CNS), pored klasičnih simptoma, mogu se javiti i glavobolje i oštećenja vida. Pacijenti sa AVP-D mogu razviti smanjenu gustinu kostiju u lumbalnoj kičmi i vratu femura. Mehanizam za ovo nije jasan. Dodatni simptomi kod pacijenata sa AVP-D mogu uključivati nespecifične simptome kao što su slabost, letargija, umor i bolovi u mišićima.

Pre sprovođenja funkcionalnog testiranja potrebno isključiti je druga stanja kod kojih se javljaju pojačan osećaj žeđi i mokrenje. Dijagnoza se postavlja na osnovu hipotonične poliurije, uz prisustvo hiperosmolalne plazme. Koncentracija natrijuma u plazmi je na gornjoj granici normale u kranijalnom i nefrogenom DI, ali je snižena u primarnoj polidipsiji.

Insipidni dijabetes treba razlikovati od primarne polidipsije, u kojoj takođe postoji problem prekomernog unosa tečnosti i posledične poliurije, ali je nivo ADH normalan. Za dijagnozu i diferencijalnu dijagnozu se koristi kratki (osmočasovni) i produženi test deprivacije vode (test žeđanja), nakon čega se primenjuje DDAVP i.m. u dozi od 2mcg (u cilju otkrivanja porekla insipidnog dijabetesa, kranijalno ili nefrogeno), uz dalje praćenje osmolalnosti urina (Tabela br 2.). Pre testa je potrebno potvrditi normalnu funkciju štitaste i nadbubrežnih žlezda (s obzirom na to da hormoni štitaste žlezde i kortizol utiču na bilans vode i elektrolita). Ukoliko osmolalitet urina ostane nizak to implicira da postoji problem sa stvaranjem ADH. Ako nakon primene dezmopresina osmolalnost urina poraste >750mOsm/kg tada je prisutan centralni diabetes insipidus. Međutim, ukoliko nakon primene dezmopresina izostane porast osmolalnosti urina znači da je odgovor na ADH neadekvatan, što upućuje na nefrogeni DI. Često je teško razlikovati da li se radi o parcijalnom DI ili primarnoj polidipsiji, posebno nakon operacije hipofize (u slučaju da pacijent nema očuvan osećaj žeđi). U ovom slučaju natrijum u plazmi i osmolalnost plazme mogu biti od pomoći, u prisustvu poliurije, jer je kod PP natrijum često nizak bazno (<135mmol/L), uz nisku osmolalnost plazme (<280 mOsm/kg), dok je u DI nivo Na viši (> 147 mmol/L), uz hiperosmolalnost plazme (>300mOsm/kg).

Tabela broj 2. Interpretacija testa deprivacije vode

Dijagnoza	Osmolalnost urina (mOsm/kg) nakon testa žeđanja	Osmolalnost urina (mOsm/kg) nakon primene dezmopresina
Normalno	>750	>750
Centralni DI	<300	>750
Parcijalni DI/ 1° polidipsija	300-750	<750
Nefrogeni DI	<300	<300

Očekivano tokom kratkog testa žeđanja se često dobija parcijalni odgovor (jer je medula bubrega smanjene koncentracione sposobnosti), zbog čega se primenjuje produženi test žeđanja (po Milleru i Mosesu). Povećanje osmolalnosti urina za 9% ili više nakon DDAVP ukazuje na parcijalni kranijalni DI. Normalan odgovor osmolalnosti urina u prisustvu visoke osmolalnosti plazme javlja se kod bolesnika sa suptilnim deficitom sekrecije vazopresina. Izostanak porasta osmolalnosti urina nakon DDAVP u prisustvu polidipsije i poliurije ukazuje na primarnu polidipsiju. Da bi se prevazišla niska senzitivnost pomenutog testa u dif dg PP i parcijalnog CDI predloženo je direktno merenje plazma AVP. Koncentracije AVP ispod normalnih ukazuju na CDI, iznad normalnih na nefrogeni DI, a normalnih vrednosti na PP. Međutim, brojni faktori su onemogućili da se određivanje AVP implementira u kliničku praksu, te je predloženo merenje kopeptina koji se sekretuje u ekvimolarnim koncentracijama. Nestimulisane vrednosti kopeptina su korisne u dif dg nefrogenog od centralnog DI (>21.4 pmol/L; 100% senzitivnost i specifičnost za potvrdu nefrogenog DI), dok je zbog značajnog preklapanja za dif dg PP i CDI potrebno uraditi stimulacioni test infuzijom hipertoničnog rastvora NaCl (Sol 3% NaCl). Stimulisane vrednosti plazma kopeptina <4.9pmol/l ukazuju na CDI (parcijalni ili totalni), dok nivo veći ili jednak 4.9pmol/L potvrđuje PP.

Magnetna rezonanca (MRI) se često koristi kod pacijenata kod kojih postoji sumnja na centralni DI. Dugo se smatralo da je odsustvo područja hiperintenziteta u zadnjoj hipofizi, takozvane svetle tačke, patognomično za CDI, jer se veruje da je rezultat AVP uskladištenog u neurosekretornim granulama. Međutim, odsustvo svetle tačke je potvrđeno kod 70% pacijenata sa CDI, ali i kod 39% pacijenata sa primarnom polidipsijom u prospektivnoj studiji koja je uključivala 92 pacijenta sa poliurijsko-polidipsičnim sindromom. Kod nekih pacijenata sa CDI je postojalo prisustvo svetle tačke. Druga tipična MRI karakteristika je zadebljana drška hipofize, takođe nije specifična za CDI. Međutim, otkrivanje ovih MRI nalaza zahteva precizniju evaluaciju poremećaja hipofize i hipotalamusa.

Veoma je važno utvrditi da li se radi o centralnom ili nefrogenom insipidnom dijabetesu, jer je terapijski pristup drugačiji. Ukoliko se radi o centralnom DI, terapija izbora je dezmopresin, analog vazopresina. Kod nefrogenog DI se koriste tiazidni diuretici koji deluju na distalni tubul blokirajući kotransport natrijuma i hlorida. Povećano izlučivanje NaCl izaziva blagu hipovolemiju, što dovodi do povećane reapsorpcije natrijuma u proksimalnom sabirnom tubulu, a samim tim povećava i reapsorpciju vode. Na ovaj način se ublažava poliurija. Ukoliko se otkrije uzrok DI potrebno je lečiti osnovno oboljenje.

Ukoliko se radi o metastatskoj bolesti hipofize (nagla pojava DI, često ispad i drugih hipofiznih tropnih hormona, kod pacijenta sa dijagnostikovanom malignom bolesti) kompletna hirurška resekcija obično nije moguća jer su metastaze često difuzne i invazivne, ali je neophodna supstitucija deficitarnih ciljnih hormona i DDAVP. Operacija je indikovana kada supraselarno širenje metastaze rezultira oštećenjem optičke hijazme i pogoršanjem vida ili kada je za tačnu dijagnozu potrebna histološka potvrda selarnog tumora radi postavljanja dijagnoze primarnog tumora i izbora adekvatne terapije. Terapijski je moguće primeniti stereotaksičnu selarnu radiohirurgiju, koja predstavlja neinvazivnu i sigurnu metodu ublažavanja kompresivnih simptoma pituitarnih metastaza. Hirurška resekcija i zračenje hipofize služe u palijaciji, da bi poboljšali lokalne simptome, ali bez uticaja na preživljavanje.

Prikazali smo slučaj mladog bolesnika koji se prezentovao poliurično-polidipsičnim sindromom. U okviru sprovedenog detaljnog dijagnostičkog i diferencijalno-dijagnostičkog postupka potvrđeno je prisustvo uzročnog hematološkog oboljenja. Dijagnoza je postavljena promptno i pacijent je upućen na dalju hematološku evaluaciju. MRI selarne regije je ukazao na parcijalnu empty sellu, uz potisnutu adenohipofizu, bez bazalnog ispada tropnih hormona. Isključeni su drugi potencijalni uzroci neurohipofizitisa. Nakon sprovedene transplantacije MĆH postignuta je kompletna remisija AML, uz kompletnu remisiju parcijalnog insipidnog dijabetesa.

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PARTIAL DIABETES INSIPIDUS: COMPLEXITY IN DIFFERENTIAL DIAGNOSIS

A 43-year-old male was hospitalized at the Clinic for Endocrinology, Diabetes, and Metabolic Diseases, UKCS, in April 2024 due to polyuric-polydipsic syndrome. Upon admission, he reported that for the past two months he has been consuming a lot of fluids, and for the past month, he has been urinating frequently. He has an increased feeling of thirst during the day and night. At night, he urinates 5-8 times depending on fluid intake. During a one-day measurement at home, he drank 5500mL and urinated 7250mL. An MRI of the sellar region verified the descent of the suprasellar cistern into the sella turcica (differential diagnosis partial "empty sella"), the adenohypophysis with a CC diameter of 3mm, slightly heterogeneous structure, without clear differentiation of focal zones. The physiological hypersignal of the neurohypophysis is not differentiated, the stalk is of appropriate position and diameter. He also conducted biochemical analyses independently: adequate glucose regulation (glucose 5.06, HbA1c 5.97%), urea 5.4, Cr 105, normal electrolytes (Na 142.6, K 4.36), serum osmolality 294mOsmol/kg, urine osmolality 378mOsmol/kg, specific urine gravity 1015. He reported having hypertension for the last three years. On Norvasc 5mg therapy, his blood pressure is adequately regulated. In his family history, he mentioned that his mother had laryngeal cancer, which also affected her relatives, and his father had metastatic cancer of unknown primary origin, his sister is being treated for anemia.

The patient was in good general condition upon admission, eupnoic, acyanotic, and afebrile. Skin and visible mucous membranes were normally colored, without signs of hemorrhagic syndrome and without peripheral lymphadenopathy. Confrontation method showed no visual field defect. Cardiac and pulmonary findings were normal; BP 120/80mmHg, heart rate 72/min, without orthostasis. Abdomen soft and non-tender.

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Laboratory analyses: A pathological leukocyte formula was verified in the complete blood count (CBC), neutropenia with lymphocytosis, and mild normocytic anemia with normal platelets (high total leukocytes for the degree of neutropenia; Le 9.3 10^9/L, Ne 0.5 10^9/L, Ly 3.6 10^9/L, Hgb 111g/L, MCV 98 fL, PLT 253 10^9/L), normal CRP (1.6 mg/L), satisfactory glycemic control (glucose 5.7mmol/L, HbA1c 5.5%), mild hypercreatininemia (Cr 109 umol/L) with normal urea (urea 4.7 mmol/L), no electrolyte imbalance (Na 140 mmol/L, K 4.3 mmol/L, Cl 104 mmol/L, Ca 2.42 mmol/L, PO4 1.30 mmol/L, Mg 0.91 mmol/L), borderline ALT values (ALT 43 U/L) with normal values of other liver function tests, elevated LDH (663 U/L). Additional analyses including ACE and chitotriosidase were within normal values. Baseline hormonal status was completely normal (TSH 1.94mIU/L, fT4 14.2pmol/L, fT3 5.03pmol/L, negative organ-specific antibodies, FSH 6.0IU/L, LH 2.5 IU/L, total testosterone 14.13nmol/L, SHBG 23.8nmol/L, PRL 202mIU/L, ACTH 3.9pmol/L, cortisol 373nmol/L, IGF-1 158.6 ng/mL). A water deprivation test, during which serum osmolality increased from 298 to 305mOsmol/kg with serum Na up to 149mmol/L, while urine osmolality increased from 482 to 528mOsmol/kg. After administration of DDAVP, urine osmolality increased to 683mOsmol/kg, but due to technical reasons, two additional samples were not collected as planned by the protocol.

Based on the clinical presentation, test results, and MRI findings of the pituitary gland showing the absence of the “bright spot” in the neurohypophysis, indicative of antidiuretic hormone (ADH) deficiency in the neurosecretory granules, a diagnosis of partial diabetes insipidus was established. Desmopressin was initiated at a dose of 100 mcg (1/2 tablet) in the evening as part of the treatment regimen.

Due to the complete blood count findings, a hematologist was consulted, and due to the peripheral smear findings showing 16% blasts and 38% cells of the monocytic lineage, the patient was urgently transferred to the Clinic for Hematology UKCS, where a diagnosis of acute myeloid leukemia with neuroleukemia was established. Specific oncological treatment was initiated, which was accompanied by complications such as bone marrow aplasia and pulmonary aspergillosis. Finally, in September 2024, after screening the International Registry, a donor was found and an unrelated allogeneic HSC transplant was performed without complications. Prior to this, therapeutic irradiation of the CNS (craniospinal axis) was conducted as part of the pre-transplant protocol. Control myelogram indicates complete remission.

Discussion

Diabetes insipidus (DI) is a disorder characterized by excessive urine output (>3L/24h) of hypoosmolar urine (<300mOsm/kg). Under physiological conditions,

if osmolality falls below 280 mOsm/kg, vasopressin secretion is suppressed, leading to the excretion of hypoosmolar urine (<100 mOsm/kg). In healthy individuals, the osmolality level at which maximum antidiuresis occurs (295mOsm/kg) is also the thirst threshold. When plasma osmolality exceeds this threshold, vasopressin is secreted, resulting in maximum urine concentration in the renal medulla.

There are central diabetes insipidus (caused by decreased synthesis of antidiuretic hormone; 80% of arginine vasopressin-secreting neurons must be damaged to cause DI) and nephrogenic DI (caused by renal resistance to circulating ADH). Due to frequent confusion between Diabetes insipidus and Diabetes mellitus, in 2022, upon the proposal of numerous European and global endocrinology associations and with the support of patients, the terminology was changed. Central DI was renamed "Arginine Vasopressin Deficiency (AVP-D)" and nephrogenic DI to "Arginine Vasopressin Resistance (AVP-R)."

Central diabetes insipidus is a rare endocrine disorder affecting nearly 1 in 25,000 people or about 0.004% of the general population. It occurs equally in both genders and can develop at any age, with hereditary forms appearing earlier in life.

Antidiuretic hormone (ADH, arginine vasopressin (AVP)) is a nonapeptide synthesized as a preprohormone (prepropressophysin) primarily in the supraoptic nuclei and to a lesser extent in the paraventricular nuclei of the hypothalamus. It is then transported via axons to the neurohypophysis, where it is stored in secretory granules and released into the systemic circulation. Before secretion, the preprohormone is enzymatically cleaved into neurophysin and copeptin, which are biologically inert, and the active hormone AVP. These components are released into the plasma in equimolar concentrations.

The primary role of ADH is to maintain osmotic balance. Hyperosmolar states strongly stimulate ADH secretion. Osmoreceptors in the anterior hypothalamus are sensitive to changes in blood osmolality. ADH primarily acts on the kidneys by binding to V2 receptors in the distal and collecting tubules, initiating an intracellular phosphorylation cascade that leads to the phosphorylation of aquaporin-2 and subsequent water reabsorption. Increased ADH production is also induced by hypovolemia. Baroreceptors in the left atrium, carotid artery, and aortic arch detect changes in blood volume and directly stimulate ADH secretion through the vagus nerve. ADH then binds to V1 receptors on the smooth muscle cells of blood vessels, initiating phosphorylation processes. The overall effect of this signaling cascade is the contraction of smooth muscle cells in blood vessels, leading to increased total peripheral resistance and, consequently, increased blood pressure.

There are congenital and acquired factors that can lead to central diabetes insipidus (Table 1)

CONGENITAL	▪ Autosomal dominant – mutation in the AVP gene, ▪ Autosomal recessive – Wolfram syndrome (mutation in the WFS1 gene)
ACQUIRED:	▪ Idiopathic – 50% ▪ Trauma – pituitary surgery, injuries, radiation therapy ▪ Primary tumors – craniopharyngioma, meningioma, germinoma, Rathke's pouch cyst, pituitary adenoma, astrocytoma ▪ Metastatic tumors – lymphomas, leukemias, breast cancer, lung cancer ▪ Inflammatory/autoimmune – lymphocytic hypophysitis, hypophysitis associated with IgG4 ▪ Vascular – hemorrhages, Sheehan's syndrome ▪ Infectious – meningitis, encephalitis, HIV, tuberculosis, toxoplasmosis ▪ Granulomatous diseases – sarcoidosis, histiocytosis ▪ Other – osmoreceptor dysfunction, hydrocephalus, drugs/toxins

About 50% of patients with central DI have an idiopathic form. Many of these patients may have autoimmune destruction of the neurohypophysis as the most likely cause of central DI.

Trauma or surgical treatment of the neurohypophysis is followed by the appearance of DI after 1-4 days. The disease can be permanent or there may be recovery that is either definitive or transient; in the latter case, recovery lasts for several days and ends with permanent DI. This triphasic pattern in the dynamics of vasopressin secretion is characteristic of traumatic DI.

Metastases to the pituitary gland represent rare complications of advanced malignant disease. In 1857, the first case of metastatic melanoma in the pituitary gland was identified through autopsy. Then, in 1913, Cushing published this unique phenomenon as a cause of diabetes insipidus. Pituitary metastases are rare, accounting for 1% of all operated pituitary tumors and <1% of all intracranial metastatic lesions. Most cases are asymptomatic and are discovered incidentally during autopsy or in patients in the terminal stage of malignant disease. For 20-30% of patients with pituitary metastases, this is the first manifestation of the malignant disease. Any type of cancer can metastasize to the pituitary gland. In women, it is most commonly breast cancer (50%), and in men, lung cancer (46%). Diabetes insipidus occurs in 50% of patients with pituitary metastases. Metastatic spread to the posterior lobe of the pituitary gland and infundibulum is a consequence of hematogenous spread through the inferior hypophyseal artery. Patients with pituitary metastases have a poor prognosis, and most die within 12 months of diagnosis.

Central diabetes insipidus (CDI) is a rare reported complication of acute myeloid leukemia (AML), occurring in less than 0.6% of AML cases. The onset of CDI typically precedes the diagnosis of AML by 1-2 months. However, CDI can occur at the time of AML diagnosis or as the initial manifestation of AML relapse. It is assumed that CDI associated with AML represents an unfavorable prognostic indicator of AML, even when CDI symptoms are alleviated by the administration of desmopressin (DDAVP). The mechanism is believed to involve leukemic infiltration of the pituitary gland, which is not always visible on MRI. In one study, as many as 61.4% of patients with CDI due to AML did not have changes on MRI, while autopsy revealed that 46% of AML patients had peripituitary leukemic infiltration in the absence of obvious CDI. Recently, several case series have indicated cytogenetic aberrations of chromosomes 3 and 7 in patients with AML associated with CDI. Both aberrations result in the overexpression of ectopic viral integration 1 (EVI-1). It is assumed that overexpression of this gene interferes with hypothalamic secretion of ADH or leads to its inactivation. DI can result from infiltration, infarction, infection, hemorrhage, or thrombosis of the pituitary gland. In a study of CDI associated with AML, Ladigan and colleagues analyzed 51 cases of adults with myeloid malignancies and associated CDI. The average age of patients was 48 years, while the average age of all AML patients was 65 years. AML associated with CDI is more common in the female population (59% women) compared to a slight male predominance in all AML. Most (45/51) of these cases are de novo AML, where patients do not have a previously known primary bone marrow neoplasm. The remaining cases consist of myelodysplastic syndrome (MDS), which is a common precursor to AML, or AML transformed from aplastic anemia, MDS, or chronic myelomonocytic leukemia (CMML).

Primary symptoms common to AVP-D and AVP-R include polydipsia, polyuria, and nocturia. Polyuria is defined as urine excretion greater than 3L per day. Urine is usually most concentrated in the morning due to the lack of fluid intake during the night and increased AVP secretion during the late sleep period. As a result, the first sign of mild to moderate loss of urine concentration ability is often nocturia. However, nocturia is often nonspecific and may be secondary to other factors. In patients with central nervous system (CNS) tumors, in addition to classic symptoms, headaches and vision impairments may occur. Patients with AVP-D may develop reduced bone density in the lumbar spine and femoral neck. The mechanism for this is unclear. Additional symptoms in patients with AVP-D may include nonspecific symptoms such as weakness, lethargy, fatigue, and muscle pain. Before conducting functional testing, it is necessary to exclude other conditions that cause increased thirst and urination. The diagnosis is based on hypotonic polyuria with the presence of hyperosmolar plasma. Plasma sodium concentration is at the upper limit of normal in cranial and nephrogenic DI but is reduced in primary polydipsia. Diabetes insipidus should be differentiated from primary polydipsia, where there is also a problem of excessive fluid intake and

consequent polyuria, but the level of ADH is normal. For diagnosis and differential diagnosis, a short (8-hour) and extended water deprivation test (thirst test) is used, after which DDAVP is administered intramuscularly at a dose of 2mcg (to identify the origin of diabetes insipidus, cranial or nephrogenic) with further monitoring of urine osmolality (Table 2). Before the test, it is necessary to confirm normal thyroid and adrenal gland function (since thyroid hormones and cortisol affect water and electrolyte balance). If urine osmolality remains low, it implies a problem with ADH production. If urine osmolality increases >750mOsm/kg after desmopressin administration, central diabetes insipidus is present. However, if there is no increase in urine osmolality after desmopressin administration, it indicates an inadequate response to ADH, suggesting nephrogenic DI. It is often difficult to distinguish whether it is partial DI or primary polydipsia, especially after pituitary surgery (if the patient does not have an intact thirst sensation). In this case, plasma sodium and plasma osmolality can be helpful in the presence of polyuria, as in PP, sodium is often low basally (<135mmol/L) with low plasma osmolality (<280 mOsm/kg), while in DI, Na levels are higher (>147 mmol/L) with hyperosmolar plasma (>300mOsm/kg).

Table 2. Interpretation of water deprivation test

Diagnosis	Urine osmolality (mOsm/kg) after the thirst test	Urine osmolality (mOsm/kg) after desmopressin administration
Normal	>750	>750
Central DI	<300	>750
Partial DI/ 1° polydipsia	300-750	<750
Nephrogenic DI	<300	<300

During a short thirst test, a partial response is often expected due to the reduced concentrating ability of the renal medulla. For this reason, the extended thirst test (according to Miller and Moses) is applied. An increase in urine osmolality by 9% or more after DDAVP administration indicates partial cranial diabetes insipidus (CDI). A normal urine osmolality response in the presence of high plasma osmolality occurs in patients with a subtle vasopressin secretion deficit. The absence of an increase in urine osmolality after DDAVP in the presence of polydipsia and polyuria indicates primary polydipsia (PP). To overcome the low sensitivity of the aforementioned test in the differential diagnosis of PP and partial CDI, direct measurement of plasma arginine vasopressin (AVP) has been proposed. AVP concentrations below normal indicate CDI, above normal suggest nephrogenic diabetes insipidus (NDI), and normal

values indicate PP. However, numerous factors have hindered the implementation of AVP measurement in clinical practice, leading to the proposal of measuring copeptin, which is secreted in equimolar concentrations. Unstimulated copeptin values are useful in the differential diagnosis of NDI versus CDI (>21.4 pmol/L; 100% sensitivity and specificity for confirming NDI), while for the differential diagnosis of PP and CDI, a stimulation test with hypertonic saline infusion (3% NaCl solution) is necessary. Stimulated plasma copeptin values <4.9 pmol/L indicate CDI (partial or total), while levels equal to or greater than 4.9 pmol/L confirm PP.

Magnetic resonance imaging (MRI) is often used in patients suspected of central DI. It was long believed that the absence of a hyperintense area in the posterior pituitary, the so-called bright spot, was pathognomonic for CDI, as it was thought to result from AVP stored in neurosecretory granules. However, the absence of the bright spot was confirmed in 70% of patients with CDI, but also in 39% of patients with primary polydipsia in a prospective study involving 92 patients with polyuric-polydipsic syndrome. Some patients with CDI showed the presence of the bright spot. Another typical MRI characteristic is a thickened pituitary stalk, which is also not specific for CDI. However, detecting these MRI findings requires a more precise evaluation of pituitary and hypothalamic disorders.

It is very important to determine whether it is central or nephrogenic diabetes insipidus, as the therapeutic approach differs. If it is central DI, the treatment of choice is desmopressin, a vasopressin analogue. In nephrogenic DI, thiazide diuretics are used, which act on the distal tubule by blocking sodium and chloride cotransport. Increased excretion of NaCl induces mild hypovolemia, leading to increased sodium reabsorption in the proximal collecting tubule, thereby increasing water reabsorption. This alleviates polyuria. If the cause of DI is discovered, the underlying disease needs to be treated.

If metastasis to the pituitary is present (sudden onset of DI, often with deficiency of other pituitary tropic hormones, in a patient with diagnosed malignancy), complete surgical resection is usually not possible because metastases are often diffuse and invasive, but substitution of deficient target hormones and DDAVP is necessary. Surgery is indicated when suprasellar expansion of the metastasis results in optic chiasm compression and visual impairment, or when histological confirmation of the sellar tumor is needed for the diagnosis of the primary tumor and selection of appropriate therapy. Stereotactic radiosurgery of the sellar region is a possible therapeutic option, representing a non-invasive and safe method for alleviating compressive symptoms of pituitary metastases. Surgical resection and radiation therapy of the pituitary serve palliative purposes, to improve local symptoms without affecting survival.

We presented a case of a young patient who exhibited polyuric-polydipsic syndrome. Through detailed diagnostic and differential diagnostic procedures, the presence of a causal hematological disease was confirmed. The diagnosis was promptly esta-

blished, and the patient was referred for further hematological evaluation. MRI of the sellar region revealed partial empty sella with displacement of the adenohypophysis, but no deficiencies in basal tropic hormones were observed. Other potential causes of neurohypophysitis were excluded. Following hematopoietic stem cell transplantation, complete remission of acute myeloid leukemia (AML) was achieved along with complete remission of partial diabetes insipidus.

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