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A MODERN VIEW OF THE TREATMENT OF CENTRAL DIABETES INSIPIDUS. A REVIEW OF THE NEW ARSENAL.

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Relevance. *Central diabetes insipidus is a severe disease characterized by decreased secretion of arginine vasopressin, resulting in the excretion of an inadequately large amount of hypotonic urine. The main clinical manifestation of the disease is polyuria-polydipsia syndrome, which significantly impairs the quality of life of patients. Currently, desmopressin preparations, a synthetic analogue of arginine vasopressin, are used to treat the disease, available in tablet form and intranasal sprays. Selecting the most convenient form of the drug is a prerequisite for successful treatment of the disease.*

Keywords: *central diabetes insipidus, desmopressin.*

Introduction. Diabetes insipidus is a disease characterized by the inability of the kidneys to reabsorb water and concentrate urine, which is based on a defect in the secretion or action of vasopressin and manifested by severe thirst and excretion of large amounts of dilute urine. Currently, there are 3 main types of diabetes insipidus: central (hypothalamic or pituitary, associated with impaired vasopressin secretion), nephrogenic (renal, vasopressin-resistant, characterized by an inadequate response of the kidneys to vasopressin) and primary polydipsia (a condition associated with excessive fluid intake). In addition to these types, there are also gestagenic (associated with accelerated vasopressin metabolism), functional (caused by rapid deactivation of the vasopressin receptor and a short duration of its action in children under 1 year of

age) and iatrogenic diabetes insipidus [60]. Development of the concept of diabetes insipidus Diabetes insipidus was first described several thousand years ago and was named by analogy with diabetes mellitus, or sugar urination, which was known at that time in ancient Egypt, Greece and Asia. The separation of diabetes mellitus and diabetes insipidus occurred in 1670, when Thomas Willis, an Oxford professor, noticed differences in the taste of urine in patients with polyuria compared to healthy volunteers [7, 12, 13]. He used the term "diabetes", implying polyuria, but it was this observation that led to the separation of diabetes mellitus from the less common diabetes insipidus a century later. The modern description of diabetes insipidus dates back to 1794, when Johann Peter Frank presented a clinical case of a patient "with prolonged abnormal increased excretion of sugar-free urine without concomitant renal pathology" and introduced the term "diabetes insipidus" (from the French word "insipide" - tasteless, colorless) [17]. According to available historical documentation, in 1841 Lacombe described a case of diabetes insipidus symptoms in 8 members of one family, which drew attention to the familial etiology of the disease [29], and subsequently a familial form of diabetes insipidus was described in 1892 [35]. In the following years, the connection of the hypothalamus with the development of diabetes insipidus became apparent, and in 1901 Magnus and Shaffer found that an extract from the posterior pituitary gland had vasopressor and antidiuretic activity [32]. A few years later, in 1913, Farini and van den Velden successfully used an extract from the posterior pituitary gland to treat diabetes insipidus [15, 54]. Subsequently, Bailey and Ranson described the supraoptic-pituitary tract in animals, which made it possible to link the supraoptic nucleus of the hypothalamus and the posterior lobe of the pituitary gland and to prove that damage to this tract in animals provokes the development of diabetes insipidus [4, 43]. In parallel, Camus and Roussy found that hypothalamic puncture promotes the development of polyuria with an intact pituitary gland [6]. As a result, by 1920, the conclusion was made,that diabetes insipidus is one of the variants of pituitary pathology, and this disease began to be called "hypopituitary syndrome" [34, 39]. In 1928, the German scientist De Lange was the first to note that some patients with diabetes insipidus did not respond positively to the administration of posterior pituitary extract, and in families with this pathology there was no transmission of the disease from man to man [31]. These observations were followed by an analysis by Forssman, who established that the kidneys play a leading role in the form of diabetes insipidus resistant to treatment with posterior pituitary extract [16]. Waring described patients with an "unusual syndrome" that manifested itself shortly after birth and was characterized by polyuria, polydipsia, fever, uncontrollable vomiting, high levels of serum sodium and chlorides, rapid dehydration, and the inability to excrete concentrated urine [57]. He concluded that these disorders were caused by a "specific

defect in renal tubular water reabsorption" and were more common in boys. In 1947, Williams and Henry introduced the term "nephrogenic diabetes insipidus" for a congenital syndrome characterized by polyuria and a renal concentration defect with intact vasopressin production [58]. In 1955, du Vigneaud received the Nobel Prize for the synthesis of the polypeptide hormone vasopressin. As part of his scientific work, du Vigneaud isolated both oxytocin and vasopressin, and then synthesized oxytocin in 1953, and vasopressin in 1954 [53]. Etiology, clinical picture and diagnosis of central diabetes insipidus Central diabetes insipidus (CDI) is a rare disease with a prevalence of 1:25,000 [22], which does not differ in men and women. In Russia, the prevalence of CDI is 0.004% [64]. The age of onset of the disease depends on the etiology [48].characterized by polyuria and renal concentration defect against the background of preserved vasopressin production [58]. In 1955, Du Vigneaud received the Nobel Prize for the synthesis of the polypeptide hormone vasopressin. As part of his scientific work, du Vigneaud isolated both oxytocin and vasopressin, and then in 1953 he synthesized oxytocin, and in 1954, vasopressin [53]. Etiology, clinical picture and diagnosis of central diabetes insipidus Central diabetes insipidus (CDI) is a rare disease with a prevalence of 1:25,000 [22], which does not differ in men and women. In Russia, the prevalence of CDI is 0.004% [64]. The age of onset of the disease depends on the etiology [48].characterized by polyuria and renal concentration defect against the background of preserved vasopressin production [58]. In 1955, Du Vigneaud received the Nobel Prize for the synthesis of the polypeptide hormone vasopressin. As part of his scientific work, du Vigneaud isolated both oxytocin and vasopressin, and then in 1953 he synthesized oxytocin, and in 1954, vasopressin [53]. Etiology, clinical picture and diagnosis of central diabetes insipidus Central diabetes insipidus (CDI) is a rare disease with a prevalence of 1:25,000 [22], which does not differ in men and women. In Russia, the prevalence of CDI is 0.004% [64]. The age of onset of the disease depends on the etiology [48].

Etiology of CDI

1. Congenital.
2. Family:

• autosomal dominant;
• DIDMOAD syndrome.

3. Due to developmental disorders of the brain (septo-optic dysplasia).
4. Acquired:

• traumatic (after surgical interventions and traumatic brain injuries);
• tumor (craniopharyngioma, germinoma, glioma, etc.);
• metastatic;
• due to hypoxic or ischemic brain damage;

• as a result of lymphocytic neurohypophysitis;
• granulomatous (tuberculosis, sarcoidosis, histiocytosis);
• infectious (congenital cytomegalovirus infection, toxoplasmosis, encephalitis, meningitis); • due to vascular pathology (aneurysm, vascular malformation);
• idiopathic.

The pathogenesis of diabetes insipidus is associated with impaired secretion or action of arginine vasopressin (AVP), a neurohypophyseal nonapeptide that regulates water-electrolyte balance [22, 23]. AVP is encoded by the AVP-neurophysin II gene, synthesized in the supraoptic and paraventricular nuclei of the hypothalamus as part of a complex of AVP precursors, neurophysin II, and the glycopeptide copeptin, and then secreted as AVP from neurons into the posterior pituitary gland. AVP is released by calcium-dependent exocytosis in response to stimuli such as orthostatic hypotension or the gag reflex [23]. Regulation of water-electrolyte balance by AVP is based on serum osmolality and circulating blood volume and is mediated by vasopressin type 2 receptors (V2 receptor) [18, 22, 23]. AVP binds to V2 receptors located on the basolateral membrane of the principal cells of the collecting ducts, which leads to the activation of protein kinase A, which phosphorylates aquaporins 2 - vasopressin-sensitive channels "embedded" in the apical cell membrane for water reabsorption (Fig. 1) [18, 22]. If this mechanism is disrupted, water is lost in large quantities with urine, causing dehydration and thirst [60]. The clinical picture is associated primarily with polyuria-polydipsia syndrome: patients excrete and consume from 3 to 20 liters of fluid, feel severe thirst, which can lead to a significant decrease in the quality of life. Other characteristic symptoms are weakness, fatigue, nocturia and associated sleep disorders, signs of dehydration (dry skin and mucous membranes, weight loss, low skin turgor). Arterial hypotension and tachycardia, decreased pressure in the right ventricle and pulmonary artery, and impaired consciousness are observed with severe dehydration and hypernatremia [11, 22]. Diagnosis is based on the presence and persistence of polyuria-polydipsia syndrome, confirmation of dehydration during a clinical examination of the patient, and laboratory data (hypernatremia and increased blood osmolality, decreased urine osmolality). Differential diagnosis of various forms of diabetes insipidus is performed in several stages [22, 33, 51, 60]. 1. The first stage confirms the presence of hypotonic polyuria. 2. The second stage includes a dry-eating test and a desmopressin test: the patient is asked to limit fluid intake for as long as possible; blood and urine samples are taken before, during, and after the test, the patient’s weight and blood pressure are measured, and the general condition is monitored. When urine osmolality decreases to 30 mOsm/kg, with a loss of 5% of body weight, an objectively serious condition, or at the patient’s request (unbearable thirst), the test is stopped. After stopping the test, desmopressin is administered, the patient is

allowed to eat and drink, and urine is collected again after 2 hours and 4 hours to determine osmolality. 3. At the third stage, the causes of the disease are sought.

Treatment. The main goal of treatment is to reduce the severity of thirst and polyuria to such an extent that the patient would be able to lead a normal life. Treatment should be easily tolerated and not significantly limit the patient's life, and the doses and time of taking the drugs should be selected individually [50, 63]. Water can also be considered as a means of treating diabetes insipidus, since its consumption in sufficient quantities allows for the relief of metabolic disorders [61], provided that the disease is not severe [50, 60, 61, 64].

Drugs for the treatment of central diabetes insipidus

1. Water.

2. Vasopressin analogues (desmopressin); - chlorpropamide; - carbamazepine; - clofibrate.

3. Natriuretic drugs: - thiazide diuretics; - indapamide. Desmopressin is the preferred drug for the treatment of central insipidus and the only one recommended in the Republic of Uzbekistan. Other drugs are effective only in cases where a slight decrease in diuresis can eliminate the symptoms of diabetes insipidus, which is possible with the preservation of residual secretion of vasopressin, but their administration increases the effect of desmopressin. [8, 61]. Desmopressin in the treatment of central insipidus The first attempts to use vasopressin to treat central insipidus were made as early as 1913, after obtaining an extract of the posterior pituitary gland containing vasopressin and oxytocin. The most effective was considered to be vasopressin tannate (pitressin), an oil solution, which became available for clinical use in the 1930s and was the drug of choice for the treatment of diabetes insipidus until the 1970s, i.e. before the advent of desmopressin. Pitressin had a longer action (5-6 days), but required intramuscular administration, which was painful and often accompanied by purulent complications [52]. Substitution of the 8th radical of vasopressin with the D-isomer of arginine reduced the vasopressor effect of vasopressin and provided greater (approximately 2000 times) antidiuretic activity of desmopressin than natural L-arginine vasopressin [45], which made desmopressin the most preferred drug for the treatment of diabetes insipidus [46, 47]. This synthetic analogue of vasopressin has a prolonged antidiuretic effect, a lesser vasoconstrictor and rhinostimulating effect, and resistance to vasopressinase. The ability to use smaller doses of the drug reduces the risk of developing such severe conditions as hyponatremia and convulsive syndrome. All this makes desmopressin the drug of choice for the treatment of central and gestational diabetes insipidus [25, 42, 55]. The first synthetic vasopressin preparations were created back in 1954, were mainly used intranasally and had lower efficacy and duration of action compared to pitressin [10], but given the lack of need for parenteral

administration were often more preferable [49]. Before the creation of the tablet form, the most commonly used desmopressin preparation was adiuretin (intranasal drops), but their use was accompanied by such unpleasant side effects as vasoconstriction and irritation of the nasal mucosa [52], and also created some difficulties for accurate dosing of drugs, sometimes requiring the use of nasal catheters [19]. In 1987, a tablet form of desmopressin, Minirin, was created, which has become widespread since the 1990s. in Europe [63]. Minirin (manufactured by Ferring AG) currently exists in two forms: for oral administration and for sublingual use. When taken orally, desmopressin is characterized by low bioavailability (from 1 to 5%), and taking it with food reduces bioavailability by another 40%,Therefore, it must be taken on an empty stomach, maintaining an interval of 30–40 minutes before meals, or 2 hours after meals, which is not always convenient for patients. Failure to comply with the rules for taking the drug may lead to a decrease in its effectiveness and the need to replace the drug [66]. After oral administration, the antidiuretic effect of the drug occurs within 15 minutes and lasts from 7 to 9 hours. The onset of action of the drug, determined by a decrease in the volume of urine and an increase in its osmolality, occurs 1 hour after administration [37]. The initial dose is 0.1 mg 2–3 times a day, then the dose is selected depending on the patient's needs for the drug and is on average 0.1–0.2 mg 2–3 times a day [60, 64]. Minirin is also an effective drug for the treatment of nocturnal enuresis in both children and adults [2, 9]. The sublingual form of the drug is used by dissolving under the tongue; the drug does not need to be washed down with water. The bioavailability of this form is 60% higher, and the clinical effect occurs within 15–45 minutes from the start of administration. The initial dose is 60 mcg in 2–3 doses, the average dose can range from 60 to 960 mcg/day [64]. A relatively recent form of intranasal administration of desmopressin has appeared in the form of a spray (Vazomirin manufactured by GENFA MEDICA, SA). The initial dose is 10 mcg (1 dose) 1–2 times a day, on average, patients require 10–40 mcg/day. The drug combines the accuracy of dosing and ease of use of the tablet form and the speed of onset of the clinical effect with intranasal use: the effect occurs within 15–30 minutes after administration. The duration of action of the drug is 8–24 h, and in some patients with high sensitivity to desmopressin, it is possible to use intranasal sprays only once a day [60, 61, 65], which can significantly affect patient compliance. In addition, the possibility of using the spray in high doses makes this form of drug administration the most convenient for patients with severe forms of CDI [61]. No special conditions are required for storing the drug, patients can take it with them [62, 68]. A limitation to the use of this form are diseases accompanied by swelling of the nasal mucosa, due to reduced absorption of the drug [50, 60, 64]. Like the tablet form, the intranasal spray is successfully used in urological practice for the treatment of nocturia: the use of the

drug allows to reduce the number of night awakenings by more than 50% against the background of good tolerability and the need for low doses [14, 26]. In addition, intranasal desmopressin has proven its effectiveness in renal colic, significantly reducing the intensity of pain [28]. Thus, desmopressin is currently available in the Russian Federation as an intranasal spray, in tablet form and as sublingual tablets. Parenteral administration of desmopressin is also possible (this form of the drug is not registered in the Russian Federation) 0.5–2,0 mcg subcutaneously, including in outpatients with concomitant pathology or allergies, with the therapeutic response being 5–20 times more pronounced than with intranasal administration [44]. When the dose of the drug is sufficient to maintain a stable therapeutic effect, a further increase in the dose only causes an increase in the duration of action by several hours [30, 44]. Due to individual pharmacokinetic characteristics and different sensitivity to the drug in patients, it is extremely important to determine the individual duration of action and the need for the drug based on the severity of polyuria symptoms in each patient [30, 44, 67]. To do this, after the effects of taking previous drugs have faded, the time of each urination and the volume of urine excreted are noted in the patient against the background of a free drinking regimen after taking the minimum dose of desmopressin. Usually, the volume of diuresis decreases 1-2 hours after taking the drug, and the total duration of action does not exceed 16-18 hours. As a rule, the maximum required dose rarely exceeds 0.2 mcg when taken orally or 10 mcg when administered intranasally in 2-3 doses [30, 44]. The most dangerous adverse effect during use is fluid retention and hyponatremia, in which case you should skip taking desmopressin and wait for the release of light urine, as well as a moderate feeling of thirst [50, 60, 64]. According to research, the use of an intranasal spray can more often provoke the development of hyponatremia in patients compared to the sublingual form, which, however, may also be associated with the heterogeneity of the studied patient groups by age [59]. Other drugs in the treatment of CDI Chlorpropamide, an antidiuretic drug that is not currently used. The antidiuretic effect is associated with the effect on the renal tubules and a decrease in water clearance, which made it possible to enhance the hydroosmotic effect of vasopressin, provided that its secretion was at least partially preserved [21, 41]. Despite the decrease in diuresis from 5.4–10.7 l/day to less than 2 l/day, there were no official recommendations for the use of this drug in CDI; in addition, severe adverse reactions such as severe hypoglycemia were noted [8, 50, 61]. Carbamazepine is an anticonvulsant and psychotropic drug used to treat epilepsy and mental disorders. This drug can stimulate the release of vasopressin from the posterior pituitary gland and also directly affects the renal tubules, increasing water reabsorption even in the absence of arginine vasopressin in vitro. This effect is associated with the effect on cAMP: in laboratory animals, carbamazepine promoted reabsorption and greater permeability for

water in the collecting ducts through a direct effect on the G-complex of the V2 receptor protein (vasopressin receptor type 2) and an increase in the expression of aquaporin 2 [5]. When studying the effect of carbamazepine on 6 patients with CDI who received 200–800 mg/day of the drug,All of them had a decrease in diuresis from 8–16 l/day to 1.9–6 l/day and an increase in urine osmolality from 60–120 mOsm/kg to 150–532 mOsm/kg. At the same time, the level of AVP remained undetectable, which confirms the absence of stimulation of its release or obstacle to deactivation by carbamazepine [36]. The development of hyponatremia was noted in up to 40% of cases in patients receiving carbamazepine for neurological disorders or pain syndrome [3, 5, 20, 24]. Clofibrate is a lipid-lowering agent that stimulates AVP production in patients with partial CDI [33, 38]. Treatment with clofibrate at a dose of 500 mg every 6 hours significantly decreased urea clearance from 280 ml/h to 141 ml/h and water clearance from 158 ml/h to 10 ml/h, while urine osmolality increased from 152 mOsm/kg to 317 mOsm/kg against the background of a concomitant decrease in AVP excretion in 2/3 of patients. A significant antidiuretic effect was observed even in patients with hypervolemia [38]. Thiazide diuretics can be used to treat both central and nephrogenic diabetes insipidus [1, 33]. This group of drugs affects the distal convoluted tubules, inhibiting the cotransport of sodium and chlorides. With prolonged exposure, the volume of extracellular fluid decreases, which leads to reabsorption of sodium and water in the proximal tubules of the kidneys, and ultimately decreases the amount of urine excreted [1]. Treatment of diabetes insipidus with chlorothiazide at 5-10 mg/kg/day or hydrochlorothiazide (1-2 mg/kg/day) in children with CDI was effective and safe, hospitalization for hypernatremia was required in 1/13 patients [40]. Indapamide is an antihypertensive diuretic agent, similar in molecular structure to hydrochlorothiazide and chlorpropamide and, like thiazide diuretics, affecting water reabsorption in the proximal renal tubules [48]. The use of indapamide 2.5 mg/day in CDI in one study allowed to reduce daily diuresis from 5–16 l/day to 2.3–9.2 l/day, but no significant effect was observed in patients who had not previously received treatment for CDI [27]. Conclusion The ability to choose the most convenient form of drug administration seems to be a very important condition for successful treatment and improving the quality of life of patients with CDI. Currently, desmopressin preparations are available in various forms, and one of the most convenient, effective and safe for patients is an intranasal spray.Treatment with clofibrate at a dose of 500 mg every 6 hours significantly decreased urea clearance from 280 ml/h to 141 ml/h and water clearance from 158 ml/h to 10 ml/h, while urine osmolality increased from 152 mOsm/kg to 317 mOsm/kg against the background of a concomitant decrease in AVP excretion in 2/3 of patients. A significant antidiuretic effect was observed even in patients with hypervolemia [38]. Thiazide diuretics can be used to treat both central

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