Posterior pituitary-adrenal interrelationships in the pathogenesis and treatment of diabetes insipidus syndrome

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The importance of the adrenal glands in the pathogenesis of insipidus polyuria has become increasingly evident. Studies on human subjects and experimental animals have yielded evidence of posterior pituitary hyperfunction in adrenalectomized animals and in humans after bilateral adrenalectomy. Adrenal cortical hyperactivity is, on the other hand, a general finding in diabetes insipidus patients.

Both series of experiments indicate that some adrenal cortical hormones and posterior pituitary hormones are physiological antagonists in relation to certain phases of diuresis. The antagonistic effects are primarily related to the internal shifts between the intracellular and extracellular fluid compartment which influence both the circulating plasma volume and the level of glomerular activity [3, 9, 11].

17-hydroxycorticoids increase the extracellular fluid compartment thereby rising the circulating plasma volume, the renal filtration rate and the rate of tubular urine flow.

Removal of the adrenals (preponderance of ADH activity) is followed by reverse changes: loss of water and sodium into the intracellular fluid compartment, decrease of the extracellular fluid and circulatory collapse [14].

It is, therefore, assumed that a preponderance of adrenal cortical activity, which cannot be counterbalanced by posterior pituitary hormones, is very essential in the pathogenesis of diabetes insipidus polyuria and polydipsia. The preponderance of 17-hydroxycorticoids over ADH activity, which occurs in insipidic patients, may usefully be corrected by the medical suppression of adrenal cortical activity.

In this clinic, a prolonged treatment with δ-cortisone has been used to suppress the 17-OHC by inhibiting the anterior pituitary cortico-

trophins: the polyuric syndrome of our patients was corrected simultaneously to the decrease of circulating 17-OHC.

Clinical material and methods

We report here the investigation of 6 cases of pituitarygenic diabetes insipidus:

Case No. 1. R. S., a 59 year old housewife with severe menopausal complaints. She developed diabetes insipidus at the age of 56 years. One injection of pitressin tannate in oil, containing 5 pressor units per cm^3, controlled her clinical manifestations for 5 days at the first time; afterwards pitressin was given more frequently. At the time of admission she received 5 units of pitressin every second day. When ADH treatment was withheld, she consumed (and excreted) 9–10 liters per day.

The case is very instructive since it explains many details of the complex posterior pituitary-adrenal interrelationships. At the time of admission and during the next 1½ years the etiology remained unclear. 25 days after the treatment has been completed, the patient did not drink more than 2.5–3.5 liters of water per day. The urinary specific gravity rose from 1000–1001 to 1005–1009. The control examination 4, 6 and 10 months later revealed an unexpected result: the patient consumed normal amounts of water (1.2–1.5 liter). The urinary specific gravity returned to normal values of 1015–1020. 18 months after the first admission, she was again admitted in this clinic with clinical, laboratory and roentgenological findings of bronchial lung carcinoma, central nervous system disorders and adrenal cortical insufficiency. At that time, no signs of diabetes insipidus syndrome were present.

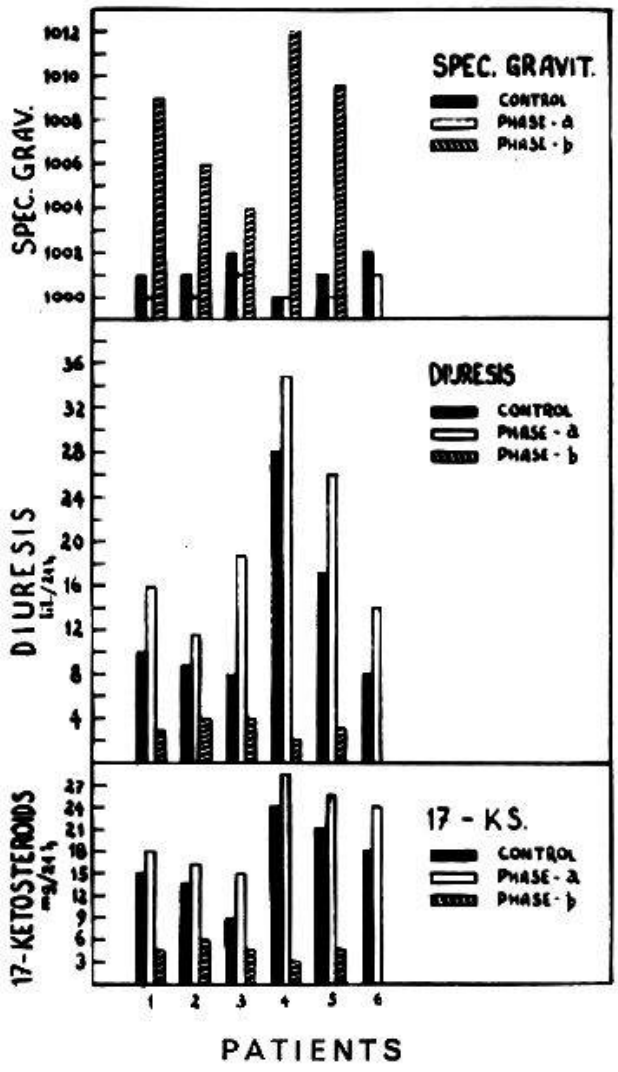
Post mortem examination[1] revealed that diabetes insipidus secondary to metastatic involvement of the hypothalamico-neurohypophysial system was the first sign of a previously unsuspected malignant lesion. Metastatic bronchial lung carcinoma, undiscovered during the first period of treatment, caused secondary diabetes insipidus. It was evident that anterior hypophysis involvement in the malignant process and consequent adrenal cortical insufficiency were a later stage of the disease. The development of adrenal cortical hypofunction was obviously potentiated by suppressive therapy of diabetes insipidus with delta cortison. Simultaneously to the decrease of adrenal cortical activity, mildering and final disappearance of diabetes insipidus syndrome was observed. (This was an equivalent to the well-known physiological fact that diabetes insipidus syndrome, experimentally induced by posterior hypophysectomy, disappears following bilateral adrenalectomy or anterior hypophysectomy.)

Case No. 2. M. B., a 50 year old female employee. The history of diabetes insipidus dates back to the age of 17 years. Etiology not clear. She maintains her water balance at 8–10 liters per day and receives no ADH treatment. Menstrual cycles still regular.

Case No. 3. V. S., a locksmith, 26 years old, developed polyglandular neuro-endocrinopathy (adiposo-genital dystrophy) and diabetes insipidus at the age of 16 years after tuberculous meningitis. His water balance varies between 8 and 9 liters. On admission, the patient received no ADH treatment.

Case No. 4. N. Z., a 25 year old autocar driver with diabetes insipidus syndrome of 6 years duration. Rheumatoid fever had developed 4 weeks before the first signs of diabetes insipidus syndrome. Allergic responsiveness to a wide variety of drugs was registered at that time. Administration of ADH preparations was followed by outstanding allergic manife tations, anuria and circulatory collapse. The patient con-

[1] Dr. *A. Premeru*, Department of Pathology of the "Dr. Dragiša Mišović Hospital", Belgrade (Yugoslavia).



sumed and excreted 20–30 liters of water per day. A period was recorded when enormous amounts up to 35–38 liters of water per day were consumed and excreted.

Case No. 5. I. M., a 42 year old housewife with diabetes insipidus syndrome of 18 years duration. At the admission she received 20 units of pitressin daily and maintained her water balance at 14–15 liters per day. When ADH treatment was withheld she consumed and excreted 16–22 liters of water per day. Etiology unclear.

Case No. 6. P. M., a 30 year old farmer with diabetes insipidus syndrome of 10 years duration. Unresponsive to ADH treatment. Etiology unclear. His water balance varied between 8–9 liters per day. He is still under the suppressive delta cortison treatment in the "polyuric" phase.

The specific gravity of urine in all patients ranged between 1000–1002. To differentiate pituitarygenic diabetes insipidus from the nephrogenic or psychogenic type, we used the antidiuretic hormone test and the water deprivation test. All patients responded rapidly to the administration of ADH. They experienced a very slight decrease in urine volumes and insignificant increase in specific gravity after 6 respectively 8 hours of the water deprivation test. A sharp increase in hematocrit and a net loss of weight was registered at the time of water deprivation. The Carter-Robbins (Hickey-Harry) test has not been used since the patient with diabetes insipidus ordinarily goes through great agony, weakness and hypothermia after hypertonic saline infusions.

To obtain maximal suppression with minimal doses, delta cortisone was given in doses of 0.5–1 mg/kg daily around-the-clock by mouth so as not to produce Cushing's syndrome. Because of the nocturnal rise in spontaneous adrenal cortical activity

(*Forsham, Di Raimondo*) it is important to give one dose of the suppressant at bedtime [7]. This form of therapy represents an around-the-clock addition of corticoids to the system. In this process the endogenous production of 17-OHC is significantly decreased. The suppressive treatment with delta cortisone was continued until 17-ketosteroid excretion decreased to 3–5 mg/24 h which required an average of 25–35 days.

The urinary 17-ketosteroids were measured by the method of *E. J. King;* for urinary 17-OHC a modification of the Reddy-Jenkins-Thorn method was used[1].

Results

During the suppressive treatment of diabetes insipidus with δ-cortisone, two different therapeutic phases could be demonstrated (fig. 1):

a) *A phase of transitory enhancement of diabetes insipidus polyuria* lasting all the time of δ-cortisone administration. The aggravation of polyuria and polydipsia is only transient and due to the diuretic properties of 17-OHC.)

In the course of δ-cortison administration, the specific gravity of urine remained at the lowest levels (1000); the volume of urine excretion rose to 50–80% of the starting values. In one case (No. 3) the 24 hour urine excretion increased from 8–9 to 18 liters. On admission, the urinary chloride excretion was decreased in all patients. The urinary 17-ketosteroids ranged between 14–23 mg/24 h in 5 cases and between 8 and 9 mg in 1 patient. The urinary output of 17-OHC was also high (15–18 mg/24 h) before the treatment started.

Under diuretic action of δ-cortisone the urinary excretion of Na, K and Cl rose; their plasma content decreased (Na: 309–320 mg%, K: 14.5 to 16.5 mg%, Cl: 340–360 mg%). The urinary output of 17-ketosteroids increased to the values of 22–29 mg/24 h during the first days of treatment; afterwards it decreased simultaneously to the degree of adrenal cortical suppression. A simultaneous increase of urinary 17-OHC to the values above 20 mg/24 h was recorded. (Important quantities of the exogenous δ-cortisone appeared in urine as Porter-Silber's chromogens impeding the appreciation of the endogenous production of 17-OHC. Since a maximum of 20% of administered cortisone appears in the urine as 11-keto-etiocholanon and 11-hydroxy-etiocholanon, it would seem reasonable to postulate that the excretion of 17-ketosteroids should provide a better index of adrenocortical suppression, at least during the time of δ-cortisone administration[2].)

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[1] Dr. *T. Drljača*, Department of Biochemistry of the "Dr. Dragiša Mišović Hospital", Belgrade (Yugoslavia).

[2] Dexamethason (9-alpha-fluoro-16-alpha-methyl prednisolon) supplies only a minor part of metabolites that interferes with endogenous adrenal cortical products; because of its potent pituitary-corticotrophin suppressing activities, it seems to be reasonable to use it in the treatment of diabetes insipidus syndrome.

b) *A phase of clinical improvement* occurring 5–7 days after the treatment has been stopped.

The thirst sensation gradually diminishes. The volume of 24 hour urine excretion decreased for 75–80% of the starting values and the specific gravity rose to 1005–1009. Plasma electrolytes returned to the normal values. The urinary 17-ketosteroids excretion decreased up to the required low values of 3–5 mg/24 h. Urinary 17-OHC excretion remained elevated until the elimination of exogenous δ-cortisone had been completed. Afterwards a gradual diminution below normal values of 6–7 mg/24 h has been found.

Water balance studies in the patient N. Z. (case No. 4) revealed a correction of more than 85%. His water intake (and urine excretion) reaching values of 35–38 liters per day was reduced to 2.5–3.5 l/24 h. The urine specific gravity rose from 1000 to 1009–1012. Urinary 17-ketosteroids decreased to very low values of 0–1.5 mg/24 h meaning a considerable suppression of adrenal cortical activity. In the next 40 days the urinary 17-ketosteroids rose again to 6–9 mg/24 h; a simultaneous elevation of water metabolism to 5–6 liters per day was also registered. A parallelism between the adrenal cortical activity and 24 hour fluid turnover was evident. The treatment of this patient is completed 3 months ago. He receives no antidiuretics any more and lives on a water turnover which varies between 4–5 liters meaning a correction of about 80%. The urinary specific gravity of this patient varies between 1005 and 1007.

One patient of this group (case No. 3) with polyglandular neuro-endocrinopathy after tuberculous meningitis had a short-lasting remission. His water balance returned to the starting values of 8–10 liters/24 h three weeks after the treatment had been stopped.

The duration of therapeutic effects of the adrenal cortical suppression and the intervals at which the hormonal treatment may be repeated is the subject of further investigation.

However, it should be emphasized that the treatment of this group of insipidic patients was completed 6–18 months ago and that they receive no antidiuretics any more. As measured by urinary output (and water intake), 70–80% correction is maintained in 4 patients. The urinary specific gravity varies between 1005 and 1009.

Discussion

The suppressive therapy of diabetes insipidus is based on the assumption that posterior pituitary and adrenal cortical hormones act antagonistically in relation to certain phases of diuresis.

Adrenal cortical hyperactivity in diabetes insipidic states is demonstrated by many clinical and experimental facts:

1. Urinary excretion of 17-ketosteroids and 17-OHC is increased in diabetes insipidus patients.

2. Histologic examination reveals hyperfunctional adrenal cortices in insipidic animals.

3. Experimental diabetes insipidus in dogs, induced by posterior hypophysectomy, is effectively corrected following bilateral adrenalectomy.

4. Diabetes insipidus polyuria is also but gradually improved when successively both the anterior and posterior pituitary gland are extirpated.

De Gennes et al. [6] reported in 1957 a case of secondary diabetes insipidus caused by metastatic lesion of the basillar skull which fully disappeared after total adrenalectomy.

A similar case of secondary diabetes insipidus arising from metastatic lung carcinoma has been reported in this paper (case No. 1). A complete remission of insipidic polyuria and polydipsia occurred simultaneously to the adrenal cortical hypofunction due to metastatic involvement of anterior hypophysis in the malignant process in a latter stage of the disease (fig. 1–4). Diabetes insipidus syndrome was only the first sign of a previously unsuspected malignant lesion.

Similar are the observations of *Warter* (1956 [14]) and of *Decourt* and *Bernard-Weil* (1957 [4]) who observed disappearance of diabetes insipidus syndrome in the course of adrenal cortical insufficiency.

Inversely, posterior pituitary hyperfunction is evidenced in adrenal cortical deficiency by many clinical and experimental facts:

1. Increased serum ADH activity after bilateral adrenalectomy (oliguria, restriction of extracellular fluid compartment, loss of water and sodium into the intracellular fluid are obviously attributable to antidiuretic hormones that act unopposed by adrenal cortical hormones).

2. Improvement of adrenal cortical insufficiency after dissecting the supra-optico-hypophysial tract.

3. Aggravation of adrenal cortical insufficiency after high doses of pitressine.

From all these experiences it is concluded that normal water balance is maintained owing to a dynamic equilibrium between the diuretic action of adrenal cortical hormones and the antidiuretic action of posterior pituitary hormones. 17-hydroxycorticoids may, therefore, exhibit a diuretic action when the extracellular fluid expansion and the increase of (GFR) becomes preponderant over relative increase in the water reabsorption rate distally [15].

The transient aggravation of polyuria and polydipsia during the first phase of treatment is due to the diuretic properties of δ-cortisone and lasts only during the administration of this drug and the period necessary for its elimination. (The transient aggravation of diabetes insipidus polyuria has, however, made some authors [9] abandon the use of synthetic corticoids in the treatment of polyuric syndromes.)

The mechanism of these diuretic effects (as well as the mechanism of diuretic effects of 11-17-oxysteroids in general) must primarily be sought in the expansion of the extracellular fluid compartment induced by increasing amounts of circulating 17-OHC (endogenous + delta cortison); this in turn will increase the effective renal plasma flow (ERPF), glomerular filtration rate (GFR) and the quantity of water delivered to the distal renal tubules. Homeostatic mechanisms of aldosteron secretion are probably also effected by the rapid changes in extracellular fluid volume. Even in normal dogs a syndrome closely resembling diabetes insipidus has been experimentally induced when massive doses of delta cortisone exceeding 50 mg/kg daily, were administered[1]. These animals excreted—and digested—excessive amounts of water which equalled 40–47% of their body weight daily.

The transient enhancement of polyuria can sometimes be very impressive and should be necessarily explained to the patient before the treatment starts.

The improvement of polyuria and polydipsia (phase 2) begins several days (5–7) after the treatment has been stopped and the exogenous 17-OHC (δ-cortisone) are completely excreted.

The amount of circulating 17-hydroxycorticoids decreases as the elimination of δ-cortisone is completely finished. The suppressive therapeutic effect is then evident: the endogenous production of 17-OHC becomes considerably lower than before the treatment due to the medical suppression of pituitary corticotrophins by δ-cortisone.

The diminution of circulating 17-OHC is followed by a mildening of polydipsia and improvement of polyuria.

The clinical and experimental data here presented indicate a considerable participation of adrenal cortex in the pathogenesis of diabetes insipidus syndrome and strongly suggest the possibility of a diabetes insipidus syndrome of "adrenal cortical" origin.

It is, therefore, assumed that both ADH deficiency (hypophysial type) as well as a preponderance of adrenal cortical activity, which cannot be counterbalanced by a normal ADH release (adrenal cortical type), are very essential in the pathogenesis of diabetes insipidus polyuria and polydipsia.

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[1] *A. Ružić:* Diabetes insipidus-like syndrome induced by massive doses of prednisone. From the Report at the 1st Meeting of the Boston Blood Club in Boston, 28 November 1956. Chairman: *W. Dameshek.*

Summary

The suppressive therapy of diabetes insipidus is based on the fact that some adrenal cortical hormones and posterior pituitary hormones are physiological antagonists in relation to certain phases of diuresis.

Clinical and experimental data presented here indicate that a preponderance of adrenal cortical activity, which cannot be counterbalanced by posterior pituitary hormones, is very essential in the pathogenesis of diabetes insipidus syndrome.

Adrenal cortical activity as measured by 24 hour—urinary 17-ketosteroids and 17-hydroxycorticoids—was increased in all insipidic patients of this group.

A prolonged treatment with δ-cortisone has been used to suppress the preponderance of adrenal cortical activity by inhibiting the anterior pituitary corticotrophins.

As shown by clinical data, the polyuric syndrome of our patients was corrected simultaneously to the decrease of circulating hydroxycorticoids.

During the treatment, two therapeutic phases could be differentiated: a) a phase of enhanced diabetes insipidus polyuria due to diuretic properties of δ-cortisone, and b) a phase of improvement after the treatment has been stopped and the administered drug is completely excreted.

As measured by urinary output, 70–80% correction has been obtained in 4 patients. The urinary specific gravity rose from 1000–1002 to 1005 to 1009. One patient is still under the treatment.

Zusammenfassung

Die Therapie des Diabetes insipidus gründet sich auf die Tatsache, daß einige Nebennierenrinden- und Hypophysenhinterlappenhormone in gewissen Phasen der Diurese physiologische Antagonisten sind.

Die hier angeführten klinischen und experimentellen Ergebnisse zeigen, daß das Überwiegen der Nebennierenrindentätigkeit, welches durch die Hypophysenhinterlappenhormone nicht ausgeglichen werden kann, in der Pathogenese des Diabetes insipidus-Syndromes eine wesentliche Rolle spielt.

Auf Grund der Bestimmung der innerhalb 24 Stunden erfolgten Ausscheidung von 17-Ketosteroiden und 17-Hydroxycorticosteroiden im Harn konnte bei allen Diabetes insipidus-Patienten dieser Gruppe eine Steigerung der Nebennierenrindentätigkeit beobachtet werden. Eine längere Behandlung mit Deltacortison galt der Dämpfung der Neben-

nierenrindentätigkeit durch Hemmung des corticotropen Hormons des Hypophysenvorderlappens.

Wie die klinischen Ergebnisse zeigten, besserte die Polyurie unserer Patienten gleichzeitig mit der Abnahme der zirkulierenden Hydroxycorticoide.

Während der Behandlung konnten zwei Phasen unterschieden werden:

a) eine Phase gesteigerter Polyurie, verursacht durch die diuretischen Eigenschaften des Deltacortisons;

b) eine Phase der Regression nach Absetzen der Therapie und dem vollständigen Ausscheiden des verabreichten Medikamentes.

Gemäß Messung der Harnmenge betrug die Besserung bei 4 Patienten 70–80%. Das spezifische Gewicht des Harnes stieg von 1000–1002 auf 1005–1009. Ein Patient befindet sich noch in Behandlung.

Résumé

Le traitement curatif du diabète insipide est basé sur le fait que certaines hormones cortico-surrénales sont des antagonistes d'hormones de la partie postérieure de l'hypophyse, dans certaines phases de la diurèse.

Des observations cliniques et expérimentales semblent montrer qu'une prépondérance d'activité cortico-surrénale, qui ne peut pas être contrebalancée par des hormones postéro-hypophysaires, est un élément essentiel dans la pathogénèse du syndrome du diabète insipide.

Une activité cortico-surrénale, mise en évidence par la détermination de l'élimination des 17-kétostéroïdes et 17-hydroxycorticoïdes en 24 heures, a été révélée par une augmentation de cette élimination chez tous les malades atteints de diabète insipide.

Un traitement prolongé avec de la delta-cortisone a été appliqué pour contrecarrer cette prépondérance de la cortico-surrénale, en inhibant les corticotrophines du lobe antérieur de l'hypophyse.

Comme l'on peut le constater dans nos observations cliniques, chez tous nos patients, le syndrome polyurique a été amélioré en relation directe avec la diminution de taux d'hydrocorticoïdes circulant.

Au cours du traitement, l'on a pu distinguer deux phases: a) une phase où la polyurie est plus forte, due aux propriétés diurétiques de la deltacortisone, et b) une phase d'amélioration, après que la thérapie a été interrompue et la drogue administrée complètement éliminée.

En se basant sur l'élimination urinaire, 70–80% d'améliorations ont été obtenues chez 4 malades. Le poids spécifique de l'urine a passé de 1000–1002 à 1005–1009. Un malade est toujours encore en traitement.

Riassunto

La terapia curativa del diabete insipido è basata sul fatto che alcuni ormoni corticosurrenali e gli ormoni postipofisari sono antagonisti fisiologici per quanto riguarda certe fasi della diuresi.

I dati clinico-sperimentali che vengono esposti mostrano che l'elemento patogenetico essenziale nella sindrome diabete insipido è un predominio dell'attività corticosurrenale, non controbilanciato dagli ormoni postipofisari.

In tutti i pazienti di questo gruppo affetti da diabete insipido si notava un aumento dell'attività cortico-surrenale, misurata in base all'escrezione urinaria di 17-chetosteroidi e 17-idrossicorticosteroidi nelle 24 ore.

Venne istituita una terapia di lunga durata con delta-cortisone allo scopo di sopprimere la preponderanza dell'attività corticosurrenalica attraverso l'inibizione delle corticotropine anteipofisarie.

Come mostrano i dati clinici, la sindrome poliurica dei nostri pazienti migliorò contemporaneamente alla diminuzione degli idrossicorticoidi circolanti.

Durante la cura si possono distinguere due fasi terapeutiche: a) fase di aumento della poliuria, dovuto alle proprietà diuretiche del delta-cortisone, b) fase die regressione dopo cessazione della terapia ed escrezione totale del medicamento somministrato.

Sulla base della quantità di urina emessa, quale criterio di valutazione, si ottenne un miglioramento del 70–80% in 4 pazienti. Il peso specifico dell'urina salì da 1000–1002 a 1005–1009. Un paziente si trova ancora sotto trattamento.

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