

Diabetes insipidus (DI) of central origin is caused by decreased or absent secretion of antidiuretic hormone. Neurogenic DI results from: brain tumors, neurosurgical interventions, congenital organic lesions, genetic defects, trauma, inflammatory or infiltrative processes. We describe a 19-year-old boy with a central DI caused by a sellar-suprasellar tumor. Based on characteristic history (4 years of polydipsia and polyuria), biochemical tests and imaging studies, DI was diagnosed in this boy at the age of 15 years. On his first MRI examination nodular thickening within the pituitary stalk was observed and treatment with desmopressin was started. After 4 months, MRI revealed a large tumor within a sellar-suprasellar region. Based on the characteristic localization of the tumor and increased serum concentration of biomarkers [human choriongonadotropin  $\beta$  ( $\beta$ -hCG) and alpha fetoprotein (AFP)] germ cell secreting tumor was diagnosed. The boy underwent chemo- and radiotherapy with a good outcome. Currently, at the age of 19 years, he is in remission. This patient is an example of diagnostic difficulties in case of DI, which can be caused by developing germ cell tumor. In each case of DI it is strongly advised to perform imaging studies (MRI) and repeat them when any abnormalities are found.

**Key words:** diabetes insipidus, sellar-suprasellar tumor, pituitary gland, neoplasm.

## Diabetes insipidus coexisting with sellar-suprasellar tumour – case report

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### Introduction

Diabetes insipidus (DI) is a condition caused by a partial or complete deficiency of vasopressin (ADH) or an insensitivity of renal tubules to vasopressin. The disease is rare, with a prevalence of 1 : 25,000 in both genders [1]. Central DI, resulting from the deficiency of antidiuretic hormone (ADH), can be a consequence of a defect in vasopressin-producing hypothalamic nuclei or a pathology affecting the pituitary stalk or posterior lobe. The abnormalities listed above can be a consequence of brain tumour, CNS surgery, congenital organic lesions, head trauma, inflammatory or infiltrative processes within the CNS. Vasopressin deficiency can also arise from a genetic defect or an abnormal immune reaction against hypothalamic nucleus neurons. Polydipsia and polyuria symptoms usually first occur when approx. 80% of vasopressin-secreting hypothalamic neurons are destroyed [2]. Organic lesions in the CNS (tumours, structural defects) account for 50% of diabetes insipidus cases in children [2]. Diabetes insipidus is characterized by excessive thirst and excretion of large volumes of diluted urine. Excessive urination also occurs during the night, which is directly linked to abnormalities in physiological nocturnal ADH secretion. Children suffering from DI are usually of a slim build and may be affected by delays in physical growth and signs of dehydration. Electrolyte abnormalities, hypernatraemia in particular, are associated with a risk of neurological disorders. The treatment of neurogenic DI involves substitution therapy with desmopressin, i.e. long-acting vasopressin analogue. As a standard, neurogenic diabetes insipidus is diagnosed when serum osmolality exceeds 300 mOsm/kg H<sub>2</sub>O and, simultaneously, urine osmolality is < 300 mOsm/kg H<sub>2</sub>O.

Germinal tumours originate from primary totipotential germ cells migrating from the yolk sac endoderm to developing gonads along the notochord. Each stage of the migration process can be affected by neoplastic transformation. Depending on the stage of differentiation and development of totipotential germ cells undergoing neoplastic change, two main cancer groups can be distinguished: pure germinoma including dysgerminoma and seminoma, which develop respectively in the ovaries and testes, and non-germinal tumours including embryonal carcinoma, yolk sac tumour, immature and mature teratoma, and mixed tumours. Aside from the central nervous system they develop along the body axis (neck, mediastinum, retroperitoneal area, sacrococcygeal region) and in the gonads. The mechanism underlying neoplastic transformation of the cells is not entirely clear. As with other tumours, a vital role is played by abnormalities in mechanisms regulating proliferation and apoptosis. The pathogenesis of intracranial germinal tumours may suggest an influence of endocrine factors which are responsible for sexual maturation. This is shown by the fact that they are located in a site responsible for regulating sexual maturation and they are more common during the period of puberty.

Intracranial germinal tumours are a heterogeneous group of neoplasms which can affect patients of any age, however, contrary to gonadal tumours (and sim-

ilarly to extragonadal tumours) they are much more common in children and adolescents. Remarkably, 90% of intracranial germinal tumours are diagnosed in patients younger than 20 years of age. The age pattern includes a peak incidence between 10 and 15 years of age. Intracranial germinal tumours account for 3-8% of all brain tumours in children [3]. Due to their histogenesis, intracranial germ cell tumours typically arise in the midline. They are usually located in the pineal gland and in the suprasellar region. The incidence ratio of pineal to suprasellar tumours is 2 : 1 [4, 5]. Between 5 and 10% of germ cell tumours involve synchronous lesions in the pineal and suprasellar regions [4]. The bifocal nature of tumour at diagnosis is most typically found in patients suffering from germinoma. It remains debatable whether bifocal lesions are a consequence of metastatic spread or independent synchronous development of the neoplastic process in two sites. Germ cell tumours also appear in other areas of the brain with a tendency to develop in the midline. These include tumours located in the IV ventricle, in the basal ganglia region and the hypothalamus. Germ cell tumours occur twice as often in men as in women [4], and peak in incidence during puberty [6]. The clinical presentation of germinal tumours varies depending on the location and size of lesions, and on the patient's age. Suprasellar dysgerminoma usually causes dysfunction of the hypothalamo-pituitary area. Typical consequences include diabetes insipidus but also isolated growth hormone deficiency or other hormonal deficiencies [4, 7]. As many as 35% of all patients with suprasellar tumour remain asymptomatic for a period exceeding six months [6]. The time lag from the first symptoms to diagnosis can thus be prolonged in this group [6], especially in patients with isolated diabetes insipidus or isolated deficiency of the growth hormone or gonadotropins. Some patients can also be affected by premature sexual development, which can occur in 5% of patients with tumour in the pituitary gland and/in the hypothalamus [6]. However, only some patients from this

group have elevated levels of free  $\beta$ -subunit of human chorionic gonadotropin ( $\beta$ -hCG) and luteinizing hormone (LH).

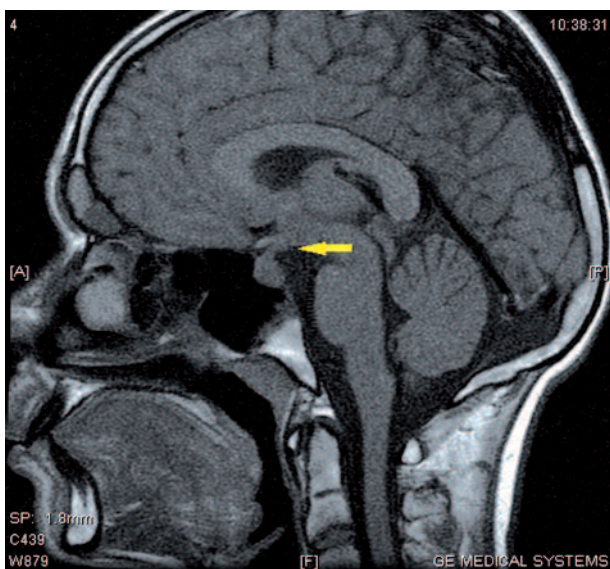
The diagnosis of germ cell tumours is mainly based on neurodiagnostic imaging (CT and MR) and determination of biomarker concentrations in blood serum and cerebrospinal fluid (AFP,  $\beta$ -hCG). For tumours which do not secrete biomarkers it is necessary to perform biopsy of the intracranial lesion to precisely determine the diagnosis [6]. Attention is often drawn to interpretative problems with head MRI scans in patients with symptoms of DI or multihormonal hypopituitarism. Lesions initially interpreted as thickening of the pituitary stalk, adenoma or lymphocytic infiltration of the pituitary gland with time prove to be germ cell tumours [8-10]. It may also happen that at the time of DI diagnosis a neoplastic lesion is too small to be identified by MRI. In these cases MR imaging needs to be repeated [3]. The diagnostic process is supplemented by measurement of the concentration of specific cancer markers:  $\beta$ -hCG, AFP, placental alkaline phosphatase (PLAP).

The aim of this work is to present the case of a boy with neurogenic DI and concomitant tumour in the sellar suprasellar region.

### Case description

A 15-year-old boy was admitted to the hospital department with suspected DI. The patient's history shows major polydipsia (6 l/24 hrs.) starting at 11 years of age, polyuria and nycturia. Head trauma suffered by the boy at 10 years old could be regarded as a possible cause of the disorders. At the time of admission, the following was found: slim body build (BMI = 18.2), normal hydration, normal physical development in the Tanner scale (Pub 4, Ax 3, G 4, testicular volume 15 ml). Additional tests revealed the following parameters: Na 145 mmol/l, K 4.7 mmol/l, urine specific gravity 1001 g/l, urine osmolality [mOsm/kg H<sub>2</sub>O] 90, serum osmolality 290 (N). The results could suggest diabetes insipidus. Persistent polyuria, considerable restlessness due to strong thirst and rapid body weight loss were observed during urine concentration test. The test ended at 5% body weight loss; the parameters were: urine specific gravity 1004 g/l, urine osmolality [mOsm/kg H<sub>2</sub>O] 150, serum osmolality 310. Following administration of a vasopressin analogue the specific gravity of urine rose to the normal level of 1020 g/l and urine osmolality to 500 mOsm/kg H<sub>2</sub>O, which confirmed the body suffered from central diabetes insipidus. Differential diagnostics excluded other causes of polyuria. Hormonal tests of pituitary function yielded results within normal range.

Magnetic resonance of the head showed an absence of high intensity signal in the posterior pituitary lobe which is characteristic for DI (lack of phospholipid compounds in the posterior lobe). The MR image revealed a nodular thickening (6 mm in diameter), intensely contrast-enhanced, within the pituitary stalk (Fig. 1). *Histiocytoma* was diagnosed. Ophthalmological consultation showed no deviations from the norm. Following neurosurgical consultation and reassessment of the MR image the suspicion of *hamartoma* of the pituitary stalk was aroused. No surgical indications were identified, though. Treatment with a vasopressin analogue was introduced, producing a good therapeutic effect.



**Fig. 1.** MRI of the head at the time of diagnosis. Sagittal projection. Apparent lack of a bright signal from the posterior pituitary lobe and nodular thickening within the pituitary stalk (arrow shows the lesion within the stalk)

After 4 months the patient was again admitted to the hospital department due to malaise persisting for several days. Physical examination showed ptosis of the upper eyelids, predominantly on the right side. No other abnormalities were identified in neurological examination. The stage of physical development was assessed in the Tanner scale: Pub 4, Ax 3, G 4 (testicular volume: 15/20 ml). Additional tests confirmed secondary hypothyroidism (fT4 = 0.17 ng/dl ↓ TSH 0.87  $\mu$ IU/ml), elevated prolactin concentration (54.97 ng/ml), elevated testosterone concentration (47 nmol/l) and low IGF-1 level (69 ng/ml) (Table 1). L-thyroxine treatment was started. Head MRI showed a large tumour in the mid-suprasellar region and a coexisting focus in the pituitary stalk previously identified by MRI (Figs. 2a-b). Based on the characteristic location of the tumour in the brain and increased concentration of biomarkers  $\beta$ -hCG (5.37 mIU/ml) and AFP (1200 IU/ml) a secreting germ cell tumour was diagnosed. The boy underwent chemotherapy which brought a nearly complete remission of the lesion. Chemotherapy consisted of four courses according to the PVB protocol. There were no indications for surgery. Local treatment involved radiation therapy to the area with tumour remnants including ventricles. The patient received a total radiation dose of 5400 cGy/t in fractional doses of 180 cGy. A follow-up MR of the head performed at the end of the therapy revealed a total regression of the neoplastic lesion including the primary nodular lesion located in the pituitary stalk (Fig. 3). At present, four years after completing therapy, the patient is in complete remission. Hormonal tests show determinants of DI, secondary hypothyroidism and growth hormone deficiency.

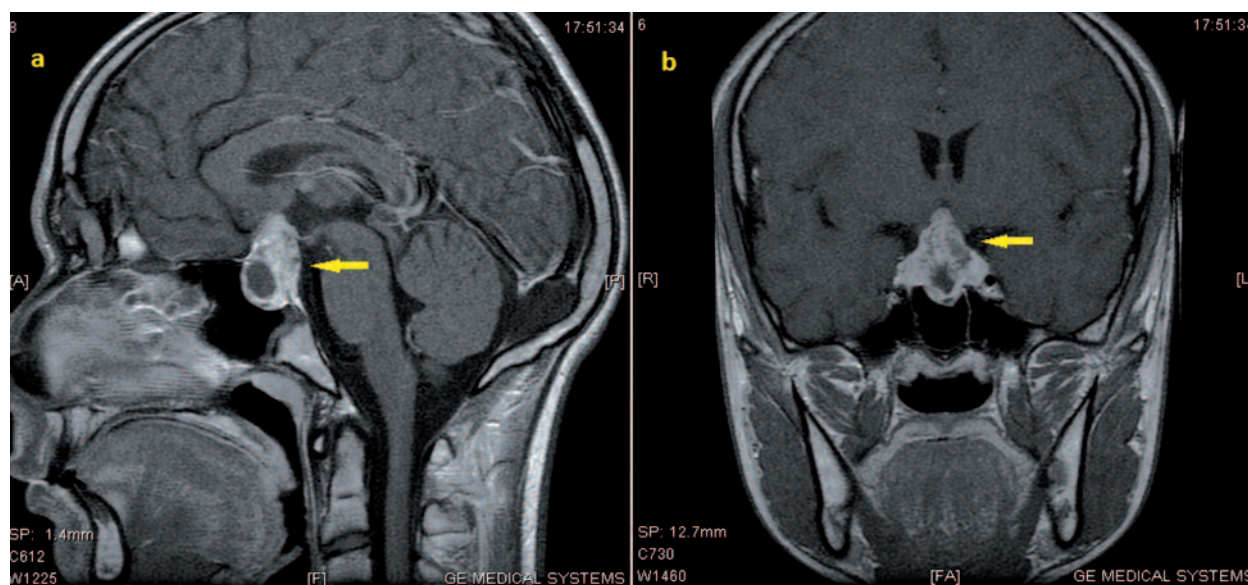
## Discussion

The case involved a patient with diabetes insipidus occurring immediately before the diagnosis of tumour of central origin and very rapidly growing germ cell tumour. It remains unsettled whether the processes are causally linked

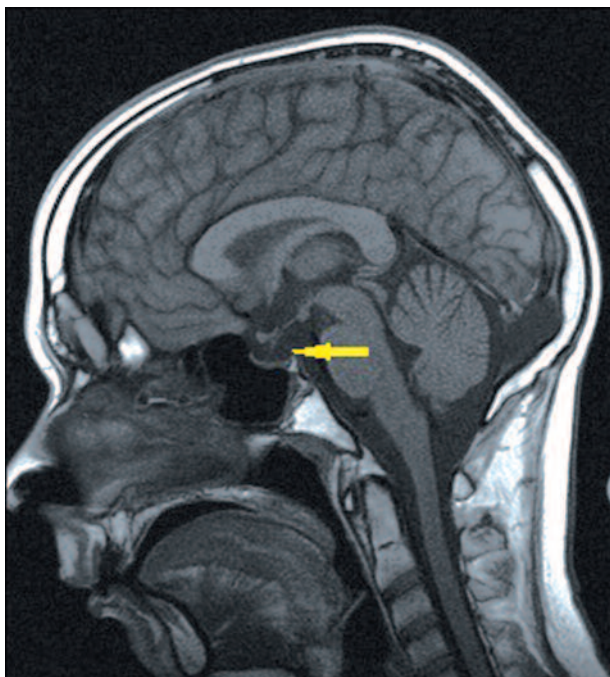
**Table 1.** Hormone levels and other biochemical parameters in blood samples at the diagnosis of sellar-suprasellar tumor

Laboratory parameter	Result	Referential value
LH (mIU/ml)	14↓	2.0-12.0
FSH (mIU/ml)	0.0↓	1.0-8.0
Prolactin (ng/ml)	54.97↑	3.28-19.68
Testosterone (nmol/l)	47.0↑	8.84-26.1
TSH ( $\mu$ IU/ml)	0.87	0.470-4.640
fT4 (ng/dl)	0.17↓	0.71-1.85
fT3 (pg/ml)	1.03↓	1.45-3.48
ACTH (pg/ml) 7.00 a.m.	16.1	10-60
Cortisol (ng/ml) 7.00 a.m.	106	94-260
DHEA-S ( $\mu$ mol/l)	6.4	2.18-12.99
IGF-1 (ng/ml)	69↓	224-592
Glucose (mg/dl)	74.0	9-101
Na <sup>+</sup> (mmol/l)	138	132-145
K <sup>+</sup> (mmol/l)	4.4	3.1-5.1
Serum osmolality (mOsm/kg H <sub>2</sub> O)	290	275-295
Urine osmolality (mOsm/kg H <sub>2</sub> O)	490	50-1400
AFP (IU/ml)	1200↑	< 5
$\beta$ -hCG (mIU/ml)	5.37↑	< 0.1

or represent two independent pathological processes. The absence of high intensity signal in the posterior pituitary lobe confirmed by MR of the head can be a manifestation of a congenital developmental defect. It is probable, however, that the lack of high intensity signal in the posterior pituitary lobe



**Fig. 2a-b.** Next MRI of the head (4 months later). Visible tumor (size 31 × 19 × 29 mm) in the sellar-suprasellar region (sagittal – 2a and frontal – 2b projection). Arrows show the tumor



**Fig. 3.** MRI of the head after chemo- and radiotherapy. The apparent total tumor regression. Residual anterior pituitary lobe

stems from a neurodegenerative process secondary to tumour growth.

Long disease history, lasting four years, preceding DI diagnosis may suggest a developmental defect. Deficiency of the antidiuretic hormone, increasing gradually from early childhood, did not show full symptoms until as late as 11 years old. The symptoms may have even lasted much longer, with mild polyuria and polydipsia not being noticed either by the patient or his parents. On the other hand, though, germ cell tumours are known to have a potentially very long period from the first symptoms until diagnosis. Another question is whether the nodular lesion in the pituitary stalk was a primary focus of the germ cell tumour or a developmental defect, a consequence of head trauma or a lymphocytic infiltration. The most likely explanation is that the lesion was a primary focus of the germ cell tumour. This suggestion is corroborated by the following facts: bifocality is one of the main attributes of germ cell tumours and regression of the lesion located in the pituitary stalk following anti-cancer therapy. The rapid progression of the neoplastic process which occurred between two MRI tests, i.e. over just four months, can be explained by the fact that in the early phase of tumour growth, when the number of cancer cells is still limited, a doubling of their number is not manifested as a considerable mass growth. With a greater number of cancer cells their doubling results in rapid mass growth.

Diabetes insipidus in the patient described seems to have been associated with neoplastic progression. Another, more probable, scenario is that an initially benign germ cell tumour – mature teratoma located in the pituitary infundibulum – became malignant and progressed rapidly.

Tumour in the mid-suprasellar region gave rise to pituitary dysfunction manifesting itself as hyperprolactinaemia,

growth hormone deficiency and thyrotropic hormone deficiency. High testosterone level can be accounted for by the stimulatory effect of high  $\beta$ -hCG concentrations. Deficiencies of the growth hormone and thyrotropic hormone persist despite chemotherapy and radiation therapy.

The clinical case presented above shows that special caution is advised in the diagnosis and monitoring of late diabetes insipidus. Furthermore, it demonstrates that MRI of the brain (pituitary region in particular) should be performed, and  $\beta$ -hCG and AFP levels determined, in each case of DI.

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