Children with Clinical Central Diabetes Insipidus at King Chulalongkorn Memorial Hospital

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Objectives: *To determine the etiologies and associated endocrine disorders in children with central diabetes insipidus (DI).*
Material and Method : *The authors retrospectively reviewed the medical records of children with central DI, who were admitted at department of Pediatrics, King Chulalongkorn Memorial Hospital, between 2000 and 2004. Aims of this study were to identify the etiology of central DI in children and also described the anterior pituitary hormone insufficiencies which may occur.*
Results: *Of the total 51 patients, 27 patients were males and 24 were females. Intracranial tumors produced DI in 36 children (70.6%), but 17 of these 36 children (47.22%) had DI before surgical removal of the tumors. Fifteen patients (29.4%) had DI from non-tumor causes, which include idiopathic in 2 patients (13.5%), terminal events in 4 patients (26.8%), central nervous system (CNS) infection in 5 patients (33.3%), CNS anomalies in 2 patients (13.5%), Kabuki syndrome in 1 patient (6.6%), head injury in 1 patient (6.6%). Anterior pituitary function was evaluated in all tumor group and 8 patients of non-tumor group. In intracranial tumor group, growth hormone deficiency (GHD) was documented in 14 from 22 patients (63.6%), secondary adrenal insufficiency in 13 from 20 patients (65%), central hypothyroid in 27 from 36 patients (75%), hyperprolactinemia in 5 from 8 patients (62.5%).*
Conclusion : *The most common etiology of central DI is intracranial tumor, and at least 50% of them have clinical features suggesting central DI before surgery. More than 60% have associated anterior pituitary hormone insufficiency.*

Keywords : *Central diabetes insipidus, Intracranial tumor*

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Central (hypothalamic, neurogenic, or vasopressin-sensitive) diabetes insipidus (DI) can be caused by various lesions including germinoma[1] and craniopharyngioma[2]; Langerhans'cell histiocytosis[2,3]; inflammatory, autoimmune, and vascular disease[4,5]; trauma resulting from surgery or an accident[6]; and in rare cases, genetic defects in the synthesis of vasopressin that are inherited as autosomal dominant or X-linked recessive trait[7-9]. In approximately 10% of children with central DI, the cause is not apparent[10,11].

Previous studies showed that the two most common causes were intracranial tumors and idiopathic[10-15]. Central DI is a rare disorder in children and adolescents. Little data have been published on the etiology and associated anterior pituitary hormone disorders. Therefore, we performed this retrospective study to determine the etiology and associated anterior pituitary hormone disorders in children with central DI.

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Material and Method

Patients

The medical records of the children with central DI admitted at King Chulalongkorn Memorial Hospital during 1st January 2000 and 31st December 2004 were retrospectively reviewed to identify the etiologies of central DI. Children with psychogenic polydipsia and nephrogenic DI were excluded. There were 51 patients (27 males and 24 females) consistent with the diagnosis of central DI.

Diagnosis and Classification of Central Diabetes Insipidus

The diagnosis of central DI was made on the basis of polyuria (urine > 4ml/kg/hr.) with diluted urine (urine sp.gr. <1.010 or urine osmolarity < 300 mOsm/L) in association with high serum osmolarity (serum osmolarity > 300 mOsm/L) and hypernatremia (serum Na > 145 mmol/L) that responds to treatment with desmopressin (DDAVP)[16]. However, the standard water deprivation test was performed in 15 patients. Computed tomograpic (CT) scanning or magnetic resonance imaging (MRI) of brain was performed in all patients in order to identify the causes of DI.

Anterior Pituitary Function

Assessment of anterior pituitary hormone was performed in 36 patients with central DI from intracranial tumors and in 8 patients from non-intracranial tumor. Growth hormone (GH) status was assessed by an insulin tolerance test (ITT). Serum GH levels were measured before and 15, 30, 45,60 and 90 minutes after the administration of insulin 0.1 unit per kilogram, given intravenously. GH deficiency was defined by peak growth hormone of less than 10 ng/ml during ITT. Corticotropin deficiency was defined by serum cortisol level of less then 20 μg/dl (550 nmol per liter) during insulin-induced hypoglycemia. All patients with intracranial tumor (36 patients) were evaluated for pituitary -thyroid axis by measuring serum levels of free thyroxine (FT4) and thyrotropin (TSH) concentrations. Central hypothyroidism was defined by serum FT4 of less than 0.8 ng/dl with low or normal TSH level.

Results

There were 51 patients, 27 patients were male and 24 female. The age at the time of diagnosis ranged from 3 days to 15 years. According to the etiology of central DI, 36 patients had intracranial tumors, 15 patients had non-tumor intracranial pathology. The chronological age at presentation ranges from 7 months to 15 years in tumor group and 3 days to 15 years in non-tumor group. The clinical manifestations of all patients are demonstrated in Table 1.

Seventeen patients with intracranial tumors (47.22%) had polyuria and polydipsia before surgical removal of tumor. After surgery, 19(52.78%) patients had signs other than polyuria or polydipsia (headache in 13 patients (36.1%), a visual defect in 21 patients (58.33%), short stature in 10 patients (27.7%), delayed puberty in 2 patients (5.5%)). Table 2 demonstrates the pathological findings; 11 patients had craniopharyngioma (30.5%), 10 patients had germ cell tumor (27.7%), 5 patients had Langerhan cell histiocytosis (13.88).

The clinical data of 15 patients with non-tumor group showed in Table 3. There were 9 male and 6 female. Polyuria and polydipsia at time of admission was demonstrated in 8 patients (53.3%), headache in 1 patient, short stature in 1 patients, precocious puberty in 1 patient. Etiology of central DI in this group include 2 patients with idiopathic, 4 patients with terminal events, 5 patients with central nervous system infection (TB meningitis in 1 case, meningoencephalitis in 1 case, brain abscess in 3 case), CNS anomalies in 2 patients, Kabuki syndrome in 1 patient, head injuries in 1 case.

DI as a terminal event were observed in 4 patients with coma and they required extensive supportive care before death. In one child, the initial cause of the hepatic encephalopathy was diagnosis. The other child had HIV infection with B-cell lymphoma with basal ganglion tumor, HIV infection with septicemia, acute non lymphocytic leukemia with septicemia.

Anterior Pituitary Function

Assessment of anterior pituitary hormone was performed in 36 patients with central DI from intracranial tumor and the results show in Table 4. Thirty six patients were evaluated for FT4 and TSH.

Table 1. Clinical characteristic of patients with central diabetes insipidus

	Intracranial tumor group	Non-tumor group
Number of patients (%)	36 (70.6)	15 (29.4)
Sex (M: F)	1:1	1.5:1
Male	18	9
Female	18	6
Age at presentation (years)		
Median	9.21	5.26
Range	7mo.-15 yr.	3 day-15 yr.
Presenting symptoms(%)		
Headache	13 (36.1)	1 (6.6)
Polyuria, Polydipsia	17 (47.2)	8 (53.3)
Impaired vision	21 (58.3)	0
Short stature	10 (27.7)	1 (6.6)
Delayed puberty	2 (5.5)	0
Precocious puberty	0	1 (6.6)
Serum Sodium (mmol/L)		
Median	156	157.6
Range	145-181	146-168
Serum Osmolality (mOsm/L)		
Median	310.4	297.2
Range	284-343	286-333

Table 2. Etiology of central diabetes insipidus from intracranial tumor

Etiology	Number of patients (%)		
	DI present before surgery	DI present after surgery	Total (%)
Craniopharyngioma	3	8	11 (30.5)
Germ cell tumor			10 (27.7)
-Immature teratoma	2	0	
-Mixed germ cell tumor	3	1	
-Germinoma	4	0	
Langerhan cell histiocytosis	4	2	6 (16.66)
Pituitary macroadenoma (Gigantism)	0	2	2 (5.55)
Pituitary adenoma	0	2	2 (5.55)
Astrocytoma	0	2	2 (5.55)
Ependymoma	1	0	1 (2.77)
Medulloblastoma	0	1	1 (2.77)
Desmoplastic neuroepithelial tumor	0	1	1 (2.77)
Total	17 (47.22%)	19 (52.78%)	36 (100%)

Table 3. Etiology of central diabetes insipidus from non- tumor group

Etiology	Number of patients (%)		
	Permanent DI	Transient DI	Total (%)
Idiopathic	2	No	2 (13.5)
Terminal event	4 (death)	No	4 (26.8)
CNS infection			
-TB meningitis	No	1	1 (6.6)
-Menigoencephalitis	1 (death)	No	1 (6.6)
-Brain abscess	3	No	3 (20)
CNS anomalies	2	No	2 (13.5)
Kabuki syndrome	1	No	1 (6.6)
Trauma (head injury)	No	1	1 (6.6)
Total	13 (86.6)	2 (13.4)	15 (100)

Table 4. Associated Endocrine disorders in patients with central DI (intracranial tumor)

	Number of patients (%)		
Endocrine disorder	before surgery	after surgery	Total (%)
GH deficiency (ITT)	6/8	8/14	14/22 (63.6)
Secondary adrenal insufficiency (ITT)	4/6	9/14	13/20 (65)
Morning cortisol			
<3 mg/dl	5/20 (25)	not done	
3-9.9 mg/dl	6/20 (30)	not done	
10-20 mg/dl	5/20 (25)	not done	
>20 mg/dl	4/20 (20)	not done	
Central hypothyroidism	11/36 (30.5)	16/36 (44.5)	27/36 (75)
Hyperprolactinemia (>25ng/ml)	5/8	not done	5/8 (62.5)

Secondary hypothyroidism was detected in 27 patients (75%) with intracranial mass, 11 patients (30.5%) had secondary hypothyroidism before tumor removal, 16 patients of 27 (59.3%) had secondary hypothyroid after surgery. Serum prolactin concentrations were high (>20 ng per milliliter) at the time of the diagnosis in 5 of 8 patients (62.5%). GH deficiency was documented in 14 patients (63.6%). All patients with growth retardation had serum growth hormone response of less than 5 ng per milliliter after insulin tolerance test.

ACTH deficiency was documented in 13 of 20 patients (65%)(before surgery 4 of 6 patients, after surgery 9 in 14 patients). All patients, who had morning cortisol level less than 3 mg/dl, were proved to have adrenal insufficiency during insulin induced hypoglycemia.

Assessment of anterior pituitary hormone was performed in 8 patients with non-tumor group. Secondary hypothyroidism was found in 3 of 8 cases (37.5%). GH deficiency and secondary adrenal insufficiency was not found in these patients. Six of them were measured for morning cortisol level and the results showed their levels were more than 10 mg/dl.

Discussion

In the present study, the most frequent etiology of central DI is intracranial tumors, followed by terminal events, brain abscess and cerebral malformation. Before surgery, the most common intracranial tumor is germinoma, which is similar to the reports from previous studies[10-16]. In contrast, patients with craniopharygioma developed central DI after surgical tumor removal. Children with intracranial tumor presented with central DI in 17 of these 36 children (47.22%) before surgery intervention and this results agree with the study by Pomarede and colleague series [13] which showed 39.7% of the children were in this category. Therefore, children presenting with DI should be carefully looked for intracranial tumor. Idiopathic DI is a diagnosis of exclusion and has been reported to occur in 27.8% to 45.2% of adults[16-20] and in 21.2% to 52.3% of children with central DI[21-23]. Two of 51 in our series were diagnosed as having idiopathic DI. Nowadays, the percentage of children with idiopathic DI is decreasing. This is probably due to the increasing in sensitivity of diagnostic imaging technique, therefore a specific etiology for at lease some patients with idiopathic central DI can now be established [21]. In addition, this study was performed as an in-patient basis, not include the patients at outpatient clinic, therefore the percentage of idiopathic DI was lower than other reports. Head trauma was an infrequent etiology in this series.

Secondary hypothyroidism was found in 27 of 36 patients (75%). Hyperprolactinemia was found in 5 of 8 patients (62.5%). Growth hormone deficiency was documented in 14 patients (63.6%). ACTH deficiency was document in 13 of 20 patients (65%). After surgery, all patients who had morning cortisol level less than 3 μg/dl showed adrenal insufficiency during insulin induced hypoglycemia. Central DI with intracranial tumor had associated anterior pituitary hormone insufficiencies more than sixty percent in our study.

In conclusion, central DI is a common presenting symptom in children with brain tumor, especially after surgical tumor removal. The most common etiologies of central DI in children and adolescents are intracranial tumor, and at least half of them have clinical manifestations with polyuria and polydipsia before surgery. Anterior pituitary function is abnormal more than sixty percent and the most common anterior pituitary deficiency is secondary hypothyroidism. Therefore, the patients should be carefully investigated before surgical intervention in order to avoid the untoward complications.

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เด็กโรคเบาจืดในโรงพยาบาลจุฬาลงกรณ์

สมลักษณ์ กฤตยารักษ์สกุล, สุทธิพงศ์ วัชรสินธุ, สุมาลี ศรีวัฒนา

วัตถุประสงค์: *ศึกษาสาเหตุและความผิดปกติทางต่อมไร้ท่อที่อาจพบร่วมด้วยในเด็กโรคเบาจืดชนิดcentral diabetes insipidus*

วัสดุและวิธีการ *เป็นการศึกษาย้อนหลังจากเวชระเบียนผู้ป่วยในที่ได้รับการวินิจฉัยโรคเบาจืดชนิด central DI ในโรงพยาบาลจุฬาลงกรณ์ตั้งแต่เดือนมกราคม พ.ศ. 2543 ถึง ธันวาคม พ.ศ. 2547 พบว่ามีผู้ป่วยทั้งสิ้น 51 ราย วัตถุประสงค์ของการวิจัยเพื่อหาสาเหตุและการเปลี่ยนแปลงทางฮอร์โมนจากต่อมใต้สมองส่วนหน้าที่อาจพบร่วมด้วย*

ผลการศึกษา: *ผู้ป่วยทั้งหมด 51 ราย เป็นเพศชาย 27 รายและเพศหญิง 24 ราย สาเหตุของ central DI จาก เนื้องอกในสมอง 36 ราย (ร้อยละ70.6) ในจำนวนนี้17ราย (ร้อยละ47.22) มีอาการcentral DI ก่อนผ่าตัดเนื้องอกสมอง สาเหตุอื่นที่ไม่ได้เกิดจากเนื้องอกสมองมี 15 ราย (ร้อยละ29.4), ผู้ป่วยระยะสุดท้ายของชีวิต 4 ราย (ร้อยละ26.8), ติดเชื้อในสมอง 5 ราย(ร้อยละ33.3), มีความผิดปกติในระบบประสาทและไม่ทราบสาเหตุอย่างละ 2 ราย (ร้อยละ13.5), กลุ่มอาการKabuki และอุบัติเหตุที่สมองอย่างละ 1 ราย (ร้อยละ 6.6) ผู้ป่วยในกลุ่มเนื้องอกสมอง ได้รับการตรวจประเมินการทำงานของต่อมใต้สมองส่วนหน้าทุกราย และในกลุ่มที่ไม่ได้เกิดจากเนื้องอกสมอง ได้รับการประเมิน 8 ราย ในกลุ่มโรคเบาจืดที่เกิดจากเนื้องอกสมองพบว่ามีภาวะบกพร่องของฮอร์โมนจากต่อมใต้สมอง ส่วนหน้าร่วมด้วยดังนี้ ขาดฮอร์โมนการเจริญเติบโต14 รายจาก 22 ราย (ร้อยละ 63.6), ขาด ACTH 13 ราย จาก 20 ราย (ร้อยละ 65), ขาดไทรอยด์ฮอร์โมนชนิดทุติยภูมิ 27 ราย จาก 36 ราย (ร้อยละ75) และ มีฮอร์โมนโปรแลคตินสูง 5 ราย จาก 8 ราย (ร้อยละ 62.5)*

สรุป: *สาเหตุพบบ่อยที่สุดของโรคเบาจืดในเด็กและวัยรุ่นคือเนื้องอกสมองเกือบครึ่งหนึ่งของผู้ป่วยจะมีอาการดื่มน้ำมาก ปัสสาวะบ่อยเป็นอาการนำตั้งแต่ก่อนผ่าตัดเนื้องอกสมอง พบความผิดปกติของต่อมใต้สมองส่วนหน้าร่วมด้วยเกินร้อยละ60 ของผู้ป่วยที่ได้รับการประเมิน*