Journal of the Formosan Medical Association (2014) 113, 102–105

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ORIGINAL ARTICLE

Endocrine dysfunction in Taiwanese children with human chorionic gonadotropin-secreting germ cell tumors

Chien-Ming Lin [a,b], Cheng-Ting Lee [a], Yi-Ching Tung [a], Mu-Zon Wu [c], Wen-Yu Tsai [a,*], Yung-Li Yang [a], Meng-Yao Lu [a], Shiann-Tarng Jou [a], Dong-Tsamn Lin [a], Kai-Hsin Lin [a]

[a] *Department of Pediatrics, National Taiwan University Hospital and College of Medicine, National Taiwan University, Taipei, Taiwan*
[b] *Department of Pediatrics, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan*
[c] *Department of Pathology, National Taiwan University Hospital and College of Medicine, National Taiwan University, Taipei, Taiwan*

Received 1 February 2012; received in revised form 12 April 2012; accepted 23 April 2012

KEYWORDS
diabetes insipidus;
human chorionic gonadotropin;
hypopituitarism;
germ cell tumors;
gonadotropin-independent precocious puberty

Background/Purpose: Human chorionic gonadotropin (HCG)-secreting germ cell tumors (GCTs) are rare childhood malignancies with unique clinical manifestations but delayed diagnosis is common. The purpose of this study is to investigate the clinical manifestations and endocrine dysfunction of Taiwanese children with HCG-secreting GCTs.
Methods: From 1991 to 2011, 24 children (19 boys and five girls) with HCG-secreting GCTs were evaluated for their clinical findings and endocrine functions.
Results: The mean age at diagnosis of the study patients was 10.8 ± 3.1 years. Of the 24 patients, 20 had central nervous system (CNS) GCTs and four had primary mediastinal GCTs (PMGCTs). The most common pathologic findings were germinomas and mixed type GCTs. The common initial symptoms and signs included polyuria, polydipsia, rapid growth, neurologic deficit,sexual precocity, and growth retardation. There was a delay in diagnosis in about 60% of patients. Diabetes insipidus and hypopituitarism were common endocrine dysfunctions in patients with CNSGCTs. Twelve boys had gonadotropin-independent puberty upon diagnosis, which were related to their high serum β-hCG levels. None of the five girls had this disorder despite their high serum β-hCG levels. Three of the four PMGCTs patients had the classic form of Klinefelter syndrome.

Conflicts of interest: The authors have no conflicts of interest relevant to this article.

* Corresponding author. Department of Pediatrics, National Taiwan University Hospital, Number 7, Chung-Shan South Road, Taipei 10002, Taiwan.
E-mail address: wenyutsai@ntu.edu.tw (W.-Y. Tsai).

doi:10.1016/j.jfma.2012.04.007

Conclusion: Taiwanese children with HCG-secreting GCTs often have clinical manifestations related to endocrine dysfunction. High index of suspicion is important to avoid delayed diagnosis in these children.

Introduction

Germ cell tumors (GCTs) are a heterogeneous group of rare tumors in childhood that may occur in gonadal and extragonadal sites like the central nervous system (CNS), retroperitoneum, or mediastinum. Overall, GCTs account for 3% of all malignant tumors in children younger than 15 years of age.1 Among extragonadal GCTs, CNSGCTs are more common than mediastinal GCTs in children.1—3 It is well known that only a small proportion of GCTs can produce β-human chorionic gonadotropin (HCG).[4] However, children with HCG-secreting GCTs have unique clinical features.

The development of gonadotropin-independent precocious puberty in boys with HCG-secreting GCTs has been reported.[5,6] Thus, GCTs may cause abnormalities in puberty that are related to their anatomic location or HCG secretion. There are very few reports on GCTs in Taiwanese children and very few children with HCG-secreting tumors are included.[4,6,7] This study was conducted to establish the clinical characteristics and endocrine dysfunction of Taiwanese children with HCG-secreting GCTs.

Participants and methods

From 1991 to 2011, there were 29 patients aged younger than 20 years who were diagnosed with HCG-secreting GCTs at the National Taiwan University Hospital. Among them, 24 who had detailed medical records for analysis were enrolled. All of them also had detectable serum HCG levels. Clinical history, physical examination, including secondary sexual characteristics, and imaging studies upon diagnosis all were examined.

Water deprivation test was done in patients with polyuria and polydipsia. Twenty patients with CNSGCTs had insulin hypoglycemia test, clonidine tolerance test, and gonadotropin-releasing hormone (GnRH) stimulation test to evaluate their anterior pituitary function according to previously reported protocols.[8—10] Serum hormone and β-hCG levels were determined by commercially available kits.

Statistical analysis

All statistical analyses was performed using the SPSS software, version 18.0 (SPSS Inc., Chicago, IL, USA). Data were compared using the non-parametric Mann-Whitney *U* test. A $p < 0.05$ was considered statistically significant.

Results

There were 24 patients (19 boys and five girls) enrolled, with a mean age at diagnosis of 10.8 ± 3.1 years (range, 5.0—15.6 years). Twenty patients had CNSGCTs and four patients had mediastinal GCTs. The common location of CNSGCTs in this study were the hypothalamic-pituitary region and distributed along the ventricular wall to the pineal region (Table 1). All five girls with GCTs had tumors located at the hypothalamic pituitary region. Nineteen patients had available histopathologic data, including germinoma in nine (47%), mixed type in eight (42%), immature teratoma in one, and choriocarcinoma in one. The histology of four patients with primary mediastinal GCTs (PMGCTs) varied from one with immature teratoma to one with choriocarcinoma, and two with mixed types, including one with mature teratoma and choriocarcinoma and the other with mature teratoma and yolk sac tumor.

The common symptoms and signs of patients with GCTs included polyuria and polydipsia in 12, rapid growth in nine, headache and vomiting in eight, abnormal gait and hemiplegia in eight, sexual precocity in five, growth retardation in four, and visual deficits in two. Two patients with PMGCTs had hemoptysis as the initial manifestation. The duration between symptom onset and diagnosis was 8.3 ± 8.1 months. Among them, 58% had symptoms longer than six months before diagnosis was made.

Except for four patients with PMGCTs, all of the other 20 patients with CNSGCTs had pituitary function evaluated. Ten patients (50%) had both diabetes insipidus (DI) and hypopituitarism. Eight patients (40%) had panhypopituitarism, and seven of them had DI (Table 2). Six patients (30%) had multiple pituitary hormone deficiency and two of them also had DI. Two other patients had isolated GHD and one of them had DI. All of the patients had GCTs infiltrating the hypothalamic-pituitary region.

Twelve boys had suppressed gonadotropin response to GnRH stimulation in the presence of elevated serum testosterone levels (range, 6.7—63.8 nmol/L). Among them, five had onset of puberty detected before the age of 9 years, which is known as gonadotropin-independent

Table 1 Tumor location in children with CNS germ cell tumors.

Tumor location	Patient number
Hypothalamic-pituitary region	7
Hypothalamus + pineal	1
Pineal	1
Hypothalamus + ventricular wall + pineal	6
Basal ganglia	3
Thalamus	1
Cerebellar vermis	1
Total	20

CNS = central nervous system.