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Clinical Study

# Re-evaluation of the significance of cerebrospinal fluid human chorionic gonadotropin in detecting intracranial ectopic germinomas

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ABSTRACT

This study was conducted to establish a reference value for cerebrospinal fluid (CSF) human chorionic gonadotropin (hCG) levels. We also evaluated the sensitivity of CSF hCG as a biomarker to detect intracranial ectopic germinomas that arise in rare sites other than the pineal and suprasellar regions. CSF hCG was measured in 201 male patients who had various types of neurological disease (not tumours of germ cell origin or other malignant tumours). A reference value of 1.009 U/L was established, and the CSF hCG level among different age groups was not significantly different. CSF and serum hCG were measured before and after radiotherapy in 14 consecutive patients with intracranial ectopic germinomas. The CSF hCG levels were all above 1.009 U/L before radiotherapy. In male patients, a CSF hCG value above 1.009 U/L suggests abnormal intrathecal hCG secretion. These results demonstrate that the CSF hCG assay is a sensitive method for diagnosing intracranial ectopic germinoma.



## 1. Introduction

Most intracranial germinomas originate from the pineal and suprasellar regions. Rarely, they arise in other regions such as the basal ganglia, thalamus, hypothalamus, corpus callosum, and the brainstem. Germinomas in these regions, which account for 5–10% of all intracranial germinomas, are well documented. We refer to these tumors as "intracranial ectopic germinomas". Unlike germinomas in the suprasellar and pineal regions, which can usually be diagnosed without difficulty, intracranial ectopic germinoma is a rare disease and relatively difficult to diagnose.

For most patients with presumed intracranial ectopic germinoma, clinical manifestation and neuroimaging findings are not specific enough to determine the diagnosis. Therefore, when an intracranial ectopic germinoma is suspected, an examination of several tumour markers, including human chorionic gonadotropin (hCG), tissue biopsy or even presumptive/diagnostic radiotherapy, is usually needed to establish the diagnosis.[1] Of all methods used to diagnose intracranial ectopic germinoma, assessment of hCG is important because it is a sensitive and specific marker for trophoblastic tumours of germ cell origin, and the assay is simple, repeatable and readily accessible.[2]

Intracranial ectopic germinomas containing syneytiotrophoblasts initially secrete hCG into the cerebrospinal fluid (CSF), then hCG diffuses into the blood. Accordingly, the CSF hCG level is elevated earlier than the serum hCG level in patients with intracranial ectopic germinomas containing syneytiotrophoblasts. Consequently, the CSF hCG level reflects the intensity of intrathecal hCG secretion and is more sensitive for the diagnosis of intracranial ectopic germinomas than the serum hCG level.[1,3–8]

Although the CSF hCG assay is widely used to diagnose intracranial tumours of germ cell origin, the normal upper limit of CSF hCG levels has not been well established. In most reports, the normal upper limit of serum hCG and hCG-β levels were used interchangeably as the CSF hCG and hCG-β levels. The most frequently used value for the normal upper limit of both CSF hCG and CSF hCG-β levels was 5 U/L.[1,3,6,9] Other studies have reported various values for the normal upper limits of CSF hCG-β levels including: 4 U/L,[8] 2 U/L,[4,10,11] 1 U/L[5,12] and 0.6 U/L.[7] However, designating the normal upper limit of serum hCG to match the CSF hCG level was arbitrary and the rationale has not been tested. In this study, a normal reference value for the CSF hCG level was established and the sensitivity of the CSF hCG assay for the diagnosis of intracranial ectopic germinomas was re-evaluated.

## 2. Material and methods

### 2.1. Determination of the CSF hCG reference value level

#### 2.1.1. Patients

This study was reviewed and approved by the Ethics Committee of the P.L.A General Hospital. Written informed consent was obtained from all participants or their guardians. Two hundred and

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one male inpatients from the neurology department were included in this study. The mean age of participants was 47.1 ± 17.4 years, ranging from 12 to 99 years. At the time of discharge, the diagnoses of these patients mainly included central nervous system (CNS) infection, inflammatory demyelinating disease, peripheral neuropathy, cerebral venous sinus thrombosis, and systematic or primary CNS vasculitis. Lumbar puncture was performed by the physicians in charge for clinical diagnostic purposes. None of the patients displayed evidence of CNS or systemic malignant tumours. Intracranial or extracranial tumours of germ cell origin had been confidently excluded.

*2.1.2. CSF hCG assay*

CSF hCG was measured on an E170 module for the Modular Analytics EVO analyser (Roche Diagnostics; Basel, Switzerland) During the assay, the CSF sample, biotinylated monoclonal hCG-specific antibodies and a monoclonal hCG-specific antibody labelled with a ruthenium complex reacted to form a sandwich complex. After the addition of streptavidin-coated microparticles, the complex bound to the solid phase via an interaction between the biotin and the streptavidin. The microparticles were magnetically captured onto the surface of the electrode and unbound substances were removed. Application of a voltage to the electrode induced a chemiluminescent emission that was measured by a photomultiplier. The results were determined via an instrument-specific calibration curve.

*2.1.3. Statistical analysis*

The CSF hCG level was expressed as a range, median, 95th percentile and 99th percentile. The 99th percentile was used to determine the normal upper limit of CSF hCG. Patients were divided into four age groups and the CSF hCG level for each age group was described and compared by the Kruskal–Wallis H test. A $p$-value < 0.05 was considered statistically significant. All statistical analyses were performed with the Statistical Package for the Social Sciences software, version 13 (SPSS Inc., Chigago, IL, USA).

*2.2. Sensitivity of the CSF hCG assay to detect intracranial ectopic germinomas*

From 1999 to 2009, the CSF hCG level in 14 patients with intracranial ectopic germinomas was measured. Diagnosis of a germinoma was confirmed by a stereotactic biopsy or open resection in four patients or by a combination of clinical factors (including neuroimaging findings and a satisfactory response to radiation) in an additional 10 patients. All patients were male, ranging from 7 to 38 years at diagnosis. The clinical data of all 14 patients are summarised in Table 1. Ten of the patients have been previously described; however, the CSF hCG reference value used in our earlier report was 5 U/L, which was also the reference value of the serum hCG level at our institute.[1] The results of the CSF hCG assay with or without the serum hCG assay, before and after radiotherapy, were described in detail. The sensitivity of the CSF hCG assay in detecting intracranial ectopic germinomas was re-evaluated using the new CSF hCG reference value established in this study.

**Table 2**
CSF hCG levels in different age groups

| Age (yrs) | $n$ | CSF hCG level (U/L) | | | | |
|---|---|---|---|---|---|---|
| | | Minimum | Maximum | Median | 95th percentile | 99th percentile |
| ⩽20 | 25 | 0.101 | 0.765 | 0.299 | 0.741 | 0.765 |
| 21–40 | 47 | <0.1 | 0.704 | 0.319 | 0.696 | 0.704 |
| 41–60 | 82 | <0.1 | 1.330 | 0.331 | 0.743 | 1.330 |
| ⩾61 | 47 | <0.1 | 0.790 | 0.329 | 0.709 | 0.790 |
| Total | 201 | <0.1 | 1.330 | 0.323 | 0.688 | 1.009 |
| $p$ = 0.608 | | | | | | |

CSF = cerebrospinal fluid, hCG = human chorionic gonadotropin, yrs = years.

## 3. Results

The CSF hCG level in all control patients ranged from <0.1 U/L to 1.33 U/L. The median, 95th percentile and 99th percentile values were 0.323 U/L, 0.688 U/L and 1.009 U/L, respectively. The CSF hCG levels reported in Table 2 revealed no statistically significant differences among four age groups ($p$ = 0.608). The 99th percentile (1.009 U/L) was considered the normal upper limit of the CSF hCG level.

Before radiotherapy, the CSF hCG level in 13 of the intracranial ectopic germinoma patients who underwent the CSF hCG assay was above 1.009 U/L. In patient 14, the CSF hCG level was not available, but the serum hCG level far exceeded the normal upper limit before radiotherapy. After radiotherapy, the CSF hCG level dropped dramatically in eight patients who underwent repetitive CSF hCG assays, with levels decreasing below 1.009 U/L in four patients (Table 3).

## 4. Discussion

Ideally, a reference value for the CSF hCG level would be established using healthy individuals. However, it is ethically unfeasible

**Table 1**
Clinical data of 14 patients with intracranial ectopic germinomas

| Patient | Age (yrs) | Sex | Symptom duration (mths) | Symptoms and signs | Tumor location |
|---|---|---|---|---|---|
| 1 | 7 | M | 27 | Right hemiparesis, diabetes insipidus, precocious puberty | Left basal ganglia, thalamus, hypothalamus, centrum semiovale |
| 2 | 14 | M | 15 | Right hemiparesis, dysarthria, mental change, diabetes insipidus, headache | Left basal ganglia, right deep white matter, left cerebellum |
| 3 | 15 | M | 5 | Nausea and vomiting, impaired cognition, nystagmus, gait imbalance | Left and right periventricular white matter |
| 4 | 13 | M | 17 | Left hemiparesis | Right basal ganglia |
| 5 | 16 | M | 6 | Right hemiparesis, diabetes insipidus | Left basal ganglia and deep white matter |
| 6 | 14 | M | 9 | Right hemiparesis | Left basal ganglia and peduncle |
| 7 | 12 | M | 4 | Extrapyramidal signs (torsion posture), mental change | Left and right basal ganglia and hypothalamus |
| 8 | 38 | M | 15 | Right hemiparesis, diabetes insipidus, headache | Left basal ganglia, thalamus and peduncle |
| 9 | 26 | M | 18 | Dysarthria, mental change, left hemiparesis | Right basal ganglia, corpus callosum |
| 10 | 15 | M | 5 | Mental change, left hemiparesis | Right basal ganglia |
| 11 | 14 | M | 37 | Weakness and intermittent pain in left extremity, slurred speech, mental change, incontinence | Left and right basal ganglia |
| 12 | 11 | M | 20 | Impaired memory, right hemiparesis | Left and right basal ganglia |
| 13 | 17 | M | 8 | Right facial paresis, right hemiparesis, diabetes insipidus, headache | Left basal ganglia, thalamus, hypothalamus |
| 14 | 15 | M | 12 | Right hemiparesis | Left basal ganglia |

M = male, mths = months, yrs = years.