

## Cerebral Germinoma with Syncytiotrophoblastic Giant Cells: Feasibility of Predicting Prognosis Using the Serum hCG Level

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### Summary

As the biological behaviour of germinoma with syncytiotrophoblastic giant cells (STGC) is not well established, the present study was undertaken to ascertain the prognostic significance of serum hCG level in affected patients. Of a total of 23 cases studied, 12 patients were regarded as pure germinomas and 11 were germinomas with STGC. All but one of the former demonstrated an excellent outcome. The exception developed subarachnoid metastases, but the tumour disappeared on radiation therapy and the patient is enjoying a normal social life 13 years after the initial treatment. With the germinoma complicated by STGC, 3 cases showed local recurrence which were followed by a poor outcome. Their pretreatment hCG levels were 15.0, 26.0 and 29.6 mIU/ml respectively. The study showed a tendency, in germinomas with STGC, for a positive association between serum hCG, and the likelihood of a poor outcome. Germinomas with STGC and serum hCG levels higher than 15 mIU/ml thus have a high recurrence rate, and more aggressive treatment is indicated for the affected patients.

**Keywords:** Germ cell tumor; syncytiotrophoblastic giant cell; human chorionic gonadotropin (hCG); outcome.

### Introduction

When patients with germinomas show mild elevation of human chorionic gonadotropin (hCG) levels in the serum or cerebrospinal fluid (CSF), they are generally regarded as germinoma with syncytiotrophoblastic giant cells (STGC) [1, 2], as confirmed from the pathological viewpoint, these cases are considered as being consistent with those in which small amounts of STGC are observed in germinoma as reported by Zaluski *et al.* [2]. Although this type of tumour is not unusual clinically, there have been few reports focused on their biological characteristics, and there is only a limited amount of information on which to base an appropriate choice of treatment. The aim of the present study is to find out whether the recurrence and prognosis of this tumour differ from those of pure ger-

minomas and whether mild elevation of serum hCG level can predict the outcome.

### Patients and Methods

Twenty three patients with germinomas, with or without mild increase of serum hCG, diagnosed by neuro-imaging or from examination of surgically resected specimen were the subject of the study. Cases positive for tumour markers such as alpha-fetoprotein, carcino-embryonic antigen or with a high serum level of hCG (> 2000 mIU/ml) were excluded. Of the total, 13 of the patients were male and 10 were female. Their ages ranged from 5 to 22 years (mean 14.8 years), and 19 (82.6%) of them were between 10 and 19 years of age. In 9 cases, histology specimens proved the diagnosis to be that of pure germinomas. The locations were in the pineal region in 13 cases and the suprasellar region in 8, and 2 cases showed tumours in both sites. All tumours demonstrated marked contrast enhancement on CT and MRI examination. All cases were treated by radiation as the initial treatment in which tumour doses of 160–200 cGy/day for a total of 50–60 Gy of fractionated linear irradiation were given. All but one of the tumours disappeared on chemotherapy with cisplatin. All the cases were followed-up for between 14 months and 13 years, with an average of 6 years. In 12 cases serum hCG was within normal range, and in 11 cases it showed mild elevation varying from 1.0 to 29.6 mIU/ml. Human chorionic gonadotropin was measured using a Delphia HCG Kit TR-FIA (Pharmacia K.K) for which the normal serum value is less than 0.1 mIU/ml. In our series of cases, pretreatment serum levels of hCG were evaluated for their ability to predict tumour recurrence and patient outcome.

### Results

The patients were divided into two groups in whom the pretreatment serum hCG levels were normal and with a mild increase. There were 12 cases in the former group, and 11 cases in the latter considered to have pure germinomas, and germinomas with STGC respectively. In the normal serum hCG group, 11 of 12 patients showed no recurrence and are enjoying a normal social life at present. In 1 patient, the tumour

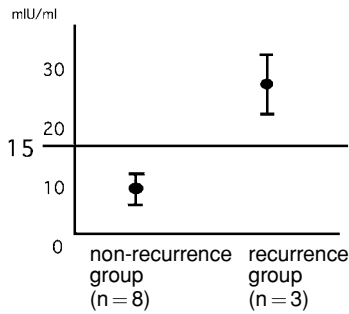


Fig. 1. Relationship between hCG titer in serum of recurrence group and non-recurrence group. It is  $7.8 \pm 6.1$  (mean  $\pm$  2SD) mIU/ml hCG in serum of non-recurrence group, and it is  $23.5 \pm 7.6$  mIU/ml in recurrence group. The two groups differ significantly ( $p < 0.001$ )

metastasised to the spinal cord and to the abdominal cavity by way of the shunt system without showing a local recurrence. The metastatic tumours were irradiated and disappeared. At the present time, 13 years after the initial treatment, the patient is alive and doing well. In the increased serum hCG group, 3 out of 11 cases suffered repeated local recurrence, accompanied by final subarachnoid dissemination of the tumour. Despite various treatments including surgery, radiation and chemotherapy, the patients succumbed 1 year, 1.5 years and 2 years after their initial treatments. Their pretreatment hCG levels were 15.0, 26.0 and 29.6 mIU/ml respectively (Table 1). The remaining 8 cases did not show recurrence and had a good outcome. Examination of the relationship between pretreatment serum hCG levels and tumour recurrence suggested 15 mIU/ml to be a border value with possi-

ble prognostic significance. None of the tumours in 8 cases with serum hCG levels below 15 mIU/ml recurred locally and the single case with remote metastases responded well to treatment. On the other hand, 3 of 5 patients with the serum hCG levels of 15 mIU/ml had relapses and a poor outcome. The intervals between the initial treatment and the recurrence were from 4 to 27 months (mean: 14 months).

## Discussion

It has been reported that germinomas with STGC recur locally more frequently than pure germinomas [3], and tend to recur earlier [4, 5]. Patients with choriocarcinomas develop local recurrence [6], extracranial metastases to the lungs, liver and lymph nodes [7, 8], and are prone to intratumoural haemorrhage, which frequently is a direct cause of death [9, 10]. More than half succumb within a year [3, 10, 11, 12, 13]. The biological behaviour of germinomas with STGC appears to lie midway between those of pure germinomas and choriocarcinomas [5]. This idea is easy to understand if it is considered together with the fact that germ cell tumours frequently have a mixed composition [13, 14], and it appears probable that the concentration of hCG in the blood depends on the amount of STGC contained in the tumour tissue. Clinical diagnostic criteria for germinoma with STGC have not yet been firmly established but, in the literature, histologically verified choriocarcinoma cases showed serum hCG levels of more than 2000 mIU/ml and many showed 10,000 mIU/ml or more [3, 8, 9, 11].

Table 1. *Primary Intracranial Germ Cell Tumour with Elevated hCG*

Case	Age/sex	hCG titer in serum (mIU/ml)	Location	Direct surgery	Shunt op.	Initial radiation (dose in Grays)	Chemotherapy (in the first care)	Recurrence	Outcome (survival in years)
1	11/F	29.6	P	+	+	W 30 + L 30	–	Regrowth	Dead (1)
2	14/M	26	P	–	–	W 40 + L 14	PBV	Regrowth	Dead (2)
3	15/F	18.0	S	–	–	L 28 + W 24	–	–	Alive (6.5)
4	18/M	15.0	P + V	–	–	L 22 + W 33	–	Regrowth Dissemination	Dead (1.5)
5	19/M	15.0	P + V	–	–	W 33 + L 22	–	–	Alive (10)
6	11/F	9.0	P	+	+	W 33 + L 22	–	–	Alive (10.25)
7	11/M	8.1	S	+	–	W 30 + L 20 + WS 20	–	–	Alive (2.25)
8	16/F	6.0	S	–	–	L 24 + W 30	–	–	*Dead (2.25)
9	12/M	4.0	P	–	–	L 20 + W 32	–	–	Alive (2.75)
10	13/M	1.0	S	+	–	W 32 + L 20	–	–	Alive (4)
11	20/F	1.0	P + V	–	–	W 36 + L 16	–	–	Alive (3)

P Pineal; S suprasellar; V ventricle; W whole brain; L local; WS whole spine; PBV cisplatin, vinblastine and bleomycin

\* Cause of death was irrelevant to brain tumour.

Many of the reported cases of germinoma with STGC had serum hCG levels above 150 mIU/ml but values exceeding 1000 mIU/ml were rare [3, 4, 13, 15]. Then, it seems reasonable that the majority of germinomas with STGC can be diagnosed clinically when the serum hCG level lies between 0.1 and 2000 mIU/ml.

Though not conclusive, the present study thus provided evidence that probability of recurrence in germinoma with STGC depends on the serum hCG level with 15 mIU/ml or above being associated with a poor outcome. The affected patients are therefore suitable for chemotherapy in addition to radiation. Mechanisms underlying the relationship between sensitivity to radiation and the amount of STGC have not been elucidated, but it has been speculated that the increase in differentiation might mean a reduction in the number of mitotic cells [16]. In addition, hCG gives rise to immunosuppression through its effects on lymphocytes, and might thereby facilitate recurrence [17]. In general, it is well recognized that the prognosis of germ cell tumours varies according to the tumour type [18, 19]. In germinomas with STGC, the present study showed a tendency that the higher the serum level of hCG, the greater the likelihood of recurrence, in line with the report of Yamagami *et al.* [17].

In conclusion, cases of germinoma with STGC in which the serum hCG level is 15 mIU/ml or more show a tendency to recur and a poor outcome, and they need more aggressive treatment than those with values less than this cutoff point.

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## Comments

This is a well-presented series of patients from Japan with germinomas. It shows quite clearly the utility of obtaining beta hCG determinations in these patients as the outcome is much worse in the patients who had elevated levels of hCG. This is excellent information, it is well presented in a short, clear paper.

*E. R. Laws*

The paper on Cerebral Germinoma by Utsuki *et al.* focuses on the prognostic significance of serum HCG levels in patients with intracranial germinomas and, in particular, those with the syncytiotrophoblastic giant cell (STGC) variety. The authors studied 23 patients – half of whom had the pure germinoma variety; the other half the STGC variety. The HCG serum levels seemed to predict fairly reliably the presence of the STGC tumour whose malignancy lies somewhere between germinoma and choriocarcinomas.

The study is straight-forward, substantiating earlier reports on the utility of serum levels of HCG as a predictor of recurrence of germinomas, in particular the more aggressive variety (STGC). It is a useful brief report for clinicians who see patients with these tumors.

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