Case Report

Basal Ganglia Germinoma Associated with Down Syndrome in a Female Patient

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Abstract

Background

Down syndrome is rarely associated with solid tumors in the central nervous system. I report on a female patient diagnosed with basal ganglia germinoma.

Patient

The study included a 15-year-old female Down syndrome patient with mild right hemiplegia. Head magnetic resonance imaging showed an intracranial mass at the left basal ganglia with a cystic component and atrophy in the left hemisphere. Human chorionic gonadotropin β-subunit level had increased. Pathological examination after endoscopic biopsy showed typical pure germinoma histology with a two-cell pattern. The patient underwent a combination therapy with chemotherapy and irradiation. At 11 months after diagnosis, she died of sepsis as a complication of chemotherapy.

Conclusion

To the best of my knowledge, this is the first report of intracranial germinoma associated with Down syndrome in a female patient.

Keywords: Germinoma; Basal Ganglia; Down Syndrome

Introduction

Down syndrome is a congenital disorder with abnormality of chromosome 21 trisomy [1,2]. Leukemia or heart malformations are common Down syndrome complications, but brain tumors are rare [3,4]. Germ cell tumors are frequent within a small number of brain tumors in patients with Down syndrome [5,6]. To the best of my knowledge, this paper reports the first case of pure germinoma at the basal ganglia in a female with Down syndrome. This manuscript presents the case history of the patient and literature review.

Case Report

A 15-year-old left-handed female with Down syndrome complained of mild right hemiplegia. The movement of the right extremities gradually diminished during the previous one year. No abnormal deep tendon reflex, heart malformation, or other heart disorders were observed. She had experienced precocious puberty at five years of age without obvious intracranial lesion (data not shown) and had received hormonal medication for five years. Horizontal nystagmus was usually observed without dizziness. The serum hormone levels, including growth hormone, insulin-like growth factor-I, adrenocorticotropic hormone, estradiol, prolactin, luteinizing hormone, follicle-stimulating hormone, thyroid-stimulating hormone, triiodothyronine, and thyroxin, were normal. Alpha-fetoprotein level was also normal, but human chorionic gonadotropin β-subunit level had slightly increased to 0.19 ng/mL. Head magnetic resonance imaging showed a lesion in the left basal ganglia with multiple cystic components. The lesion was distributed from the clivus to the left lateral ventricle wall (Figs. 1A–C). The left cerebral hemisphere was atrophic but was not compressed by the basal ganglia lesion. Methionine-positron emission tomography (PET) showed increased methionine uptake at the lesion (Fig. 1D). In contrast, 18F-Fluorodeoxyglucose-(FDG) PET showed no accumulation at the lesion. Further, FDG uptake was reduced in the entire left hemisphere (Fig. 1E).

Biopsy of the basal ganglia lesion was performed by endoscopic surgery through the left ventral horn approach. The specimen was obtained from the lesion on the ventricle wall. Pathological examination showed two-cell patterns comprising large cells with prominent nucleoli and small lymphocytes (Fig. 2A). Tumor cells were c-kit- and D2-40-
positive but cytokeratin (CAM5.2)- and glial fibrillary acidic protein (GFAP)-negative under immunohistochemical examination (Figs.2B–E). Immunohistochemical examination was performed by using anti-c-kit antibody (Nichirei BioScience; ready to use) (Fig.2B), anti-D2-40 antibody (Nichirei BioScience; ready to use) (Fig.2C), anti-CAM5.2 antibody (Beckman Dickinson; ready to use) (Fig.2D), and anti-GFAP antibody (Nichirei BioScience; ready to use) (Fig.2E), respectively. No nongerminomatous component was detected, and the tumor was diagnosed as pure germinoma.

The patient underwent chemotherapy using 900 mg/m² ifosfamide, 20 mg/m² cisplatin, and 60 mg/m² etoposide on days 1–5 (ICE therapy) [7]. After the second course of ICE, irradiation (30 Gy in 15 fractions by TomoTherapy) against the focal lesion and the entire ventricle was performed. The ICE chemotherapy was performed three times each a month, then the following ICE chemotherapy was performed every three months. After five courses of ICE, severe pancytopenia and septic shock developed. She was treated with granulocyte-colony stimulating factor and transfusion of red blood cells and platelets. Further, antibiotics were given. Although the best medication was given, she, unfortunately, died of multiple organ failure due to septic shock.

**Discussion**

Down syndrome is known to be associated with leukemia or congenital heart diseases [4,8-12]. In contrast, malignancy in the central nervous system (CNS) is rare in patients with Down syndrome [3,4]. To the best of my knowledge, only 22 cases of CNS germ cell tumors that are associated with Down syndrome have been reported in the last half century, including my case (Table 1) [7,13-30]. The mean age of the patients was 11.2 years (range, 0–35 years), and 17 patients were males (mean age, 11.9 years; range, 0.2–35 years), whereas the remaining 5 patients were females (mean age, 8.8 years; range, 0–17 years). Of the 22 tumors, 11 were germinomas, 6 were yolk sac tumor, and 5 were teratomas. The major tumor locations were the basal ganglia (12 cases), pineal region (5 cases), posterior fossa (4 cases), and cerebellar pontine angle (3 cases). In addition, the third ventricle, mid brain, thalamus, and spine were identified as sites of the germ cell tumor. Previous reports demonstrated that CNS germ cell tumors were diagnosed in younger patients with Down syndrome, with a high rate of yolk sac tumors (28% of whole germ cell tumors patients with Down syndrome), and were expected to be observed in the basal ganglia. In contrast to that in patients without Down syndrome, the histological diagnosis of yolk sac tumor developing at the basal ganglia or posterior fossa was much more frequent [17,19,24-26,29]. Furthermore, the ratio of germ cell tumor in intracranial malignancies was higher in patients with Down syndrome than that in the other populations [4].

The radiological findings showed atrophic cerebral hemisphere on the side of the lesion. This observation has also been reported in basal ganglia germinomas [31,32]. Wallerian degeneration by the basal ganglia germinoma caused left hemispheric atrophy.

A genetic background of 21 trisomy might contribute to germ cell tumor development in the CNS. However, the mechanism for the high frequency of germ cell tumors in patients with Down syndrome is unclear. These tumors originate from the ectopic primitive germ cells. During the normal development process, these ectopic germ cells are eliminated by the immunological system or disappear by apoptosis. Down syndrome patients reportedly have diminished immunological function or apoptosis induction systems [4,33]. Furthermore, the normal regulation of T lymphocyte proliferation gradually decreases in Down syndrome patients [34,35]. The genetic mutation of chromosome 21 trisomy can cause tumorigenesis at the intracranial germ cell tumor [36]. However, tumorigenesis is different due to the ratio of intracranial germ cell tumor formation in Down syndrome patients and the occurrence of the tumor-carrying chromosome 21 trisomy karyotype. The tumorigenesis of germ cell tumors might be caused by a different mechanism between somatic and genetic mutations of chromosome 21 trisomy. Although Down syndrome in female patients has been reported to be associated with teratoma [15,22] or yolk sac tumor [17,29], to the best of my knowledge, no previous report has described its linkage with pure germinoma or has correlated it with germinoma in the basal ganglia. I report for the first time to my knowledge the association with intracranial germinoma in a female with Down syndrome.

Combination radiation and chemotherapy was performed in 10 of the 22 reported cases. In contrast, monotherapy, with or without resection, of radiation and chemotherapy was performed in 3 and 4 cases, respectively, whereas surgical resection was performed in 2 and not performed in 2. One 4-month-old female patient received a ventricle-plural shunt system without further medications. The chemotherapies were based on platinum agents. Of the 22 patients, 11 died during medical treatment or follow-up (mortality rate, 50%). The overall mean survival rate was 8.3 months (range, 3 weeks–35 months). The patients survived for 11 months after diagnosis and therapy. The female patients with Down syndrome and intracranial germ cell tumor usually had good responses to the therapy. The female patients of a previous report were alive after combination therapy with chemotherapy and radiotherapy [17,29]. However, this case patient did not survive. Although few cases have been reported, the discrepancy of the therapeutic outcome might be due to the histological differences of yolk sac tumors and germinomas.
Table 1. Summary of the intracranial germ cell tumors in Down syndrome patients.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Report [Reference]</th>
<th>Age, Sex</th>
<th>Site</th>
<th>Histology</th>
<th>Therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Komiya (1975) [13]</td>
<td>2 y, M</td>
<td>Posterior fossa</td>
<td>Teratoma</td>
<td>No</td>
<td>Deceased (2 m)</td>
</tr>
<tr>
<td>3</td>
<td>Yamasaki (1985) [15]</td>
<td>4 m, F</td>
<td>Basal ganglia, posterior fossa</td>
<td>Teratoma</td>
<td>VP shunt</td>
<td>Deceased (7 m)</td>
</tr>
<tr>
<td>4</td>
<td>Fujita (1992) [16]</td>
<td>9 y, M</td>
<td>Basal ganglia</td>
<td>Germinoma</td>
<td>Subtotal resection radiotherapy</td>
<td>Alive (1 m)</td>
</tr>
<tr>
<td>5</td>
<td>Oshita (1993) [17]</td>
<td>12 y, F</td>
<td>Basal ganglia</td>
<td>Yolk sac tumor</td>
<td>Subtotal resection chemotherapy (CDDRVP16), radiotherapy</td>
<td>Alive (12 y)</td>
</tr>
<tr>
<td>6</td>
<td>Hashimoto (1995) [18]</td>
<td>12 y, M</td>
<td>Basal ganglia</td>
<td>Germinoma</td>
<td>Subtotal resection radiotherapy</td>
<td>Alive (17 y)</td>
</tr>
<tr>
<td>7</td>
<td>Wada (1995) [19]</td>
<td>6 y, M</td>
<td>CP angle</td>
<td>Yolk sac tumor</td>
<td>Chemotherapy (CPA, VCR, BLM, CDDP)</td>
<td>Deceased (5 m)</td>
</tr>
<tr>
<td>8</td>
<td>Nakashima (1997) [20]</td>
<td>12 y, M</td>
<td>Basal ganglia, dissemination</td>
<td>Germinoma with STGC</td>
<td>Total resection chemotherapy (CDDP, VP16), radiotherapy (WB)</td>
<td>Deceased (14 m)</td>
</tr>
<tr>
<td>10</td>
<td>Robson (1997) [22]</td>
<td>newborn, F</td>
<td>Pineal region</td>
<td>Mature teratoma</td>
<td>Total resection</td>
<td>Alive</td>
</tr>
<tr>
<td>11</td>
<td>Matsumura (1998) [23]</td>
<td>10 y, M</td>
<td>Basal ganglia, thalamus</td>
<td>Germinoma</td>
<td>Subtotal resection</td>
<td>Deceased (3 w)</td>
</tr>
<tr>
<td>12</td>
<td>Matsumura (1998) [23]</td>
<td>20 y, M</td>
<td>Pineal region</td>
<td>Germinoma</td>
<td>Subtotal resection chemotherapy (CBDCA, VP16), radiotherapy (focal)</td>
<td>Deceased</td>
</tr>
<tr>
<td>16</td>
<td>Maeda (2011) [26]</td>
<td>13 y, M</td>
<td>Basal ganglia</td>
<td>Yolk sac tumor</td>
<td>Chemotherapy (ICE) radiotherapy (CSI)</td>
<td>Alive</td>
</tr>
<tr>
<td>17</td>
<td>Satoh (2012) [27]</td>
<td>35 y, M</td>
<td>Pineal region, CP angle, spine</td>
<td>Germinoma</td>
<td>Chemotherapy radiotherapy</td>
<td>Deceased (35 m)</td>
</tr>
<tr>
<td>18</td>
<td>Bakhtiar (2012) [28]</td>
<td>2 m, M</td>
<td>Cerebellum</td>
<td>Immature teratoma</td>
<td>Subtotal resection chemotherapy (CE)</td>
<td>Alive</td>
</tr>
<tr>
<td>19</td>
<td>Sugimoto (2013) [29]</td>
<td>17 y, F</td>
<td>Basal ganglia</td>
<td>Yolk sac tumor</td>
<td>Chemotherapy (ICE) radiotherapy</td>
<td>Alive</td>
</tr>
<tr>
<td>22</td>
<td>present case (2018)</td>
<td>15 y, F</td>
<td>Basal ganglia</td>
<td>Germinoma</td>
<td>Chemotherapy (ICE) radiotherapy (focal, WB)</td>
<td>Deceased (11 m)</td>
</tr>
</tbody>
</table>
y, year; m, month; w, week; M, male; F, female; CP angle, cerebellopontine angle; STGC, syncytiotrophoblastic giant cells; VP shunt, ventricle-pleural shunt; CDDP, cisplatin; VP16, etoposide; CPA, dacarbazine; VCR, vincristine; BLM, bleomycin; WB, whole brain; CBDCA, carboplatin; ICE, ifosfamide + cisplatin + etoposide; CSI, cerebral-spinal irradiation.

**Figure 1:** Head MRI at admission
T2 weighed image (A) and fluid-attenuated inversion recovery image (B) showed the intracranial lesion with cystic components at the left basal ganglia. Solid components showed gadolinium staining (C). While methionine uptake had increased (D), 18F-FDG uptake decreased with ubiquitous decrease in the left hemispheric metabolism (E).

**Figure 2:** Pathological results of the lesion
Hematoxylin-Eosin staining showed a two-cell pattern (A). Tissue surface antigen reaction was performed by c-kit (B), D2-40 antibody (C), CAM5.2 antibody (D), and GFAP antibody (E). Pathological photos are shown by ×20 magnification.
References


