Intracranial germ cell tumors (GCTs) represent <5% of all pediatric central nervous system (CNS) tumors, and germinomas are the most frequently occurring type. Germ cell tumors have very heterogeneous findings. Its localization (unifocal or bifocal), the presence of additional pituitary dysfunction, and the long duration of symptoms in some cases may cause diagnostic confusion. Intracranial GCTs are difficult to be differentiated from various neoplastic or inflammatory diseases due to similar clinical, radiological, and even pathological findings.

We evaluated admission characteristics (clinical, biochemical, radiological, and pathological) and pituitary dysfunction of cases with intracranial GCTs between December 2014 and December 2020. In 5 cases (aged 8.7-14.8 years) diagnosed during the study period, central diabetes insipidus (CDI) was the first symptom of hypophyseal dysfunction. Duration of symptoms related to CDI before tumor diagnosis was 3 months to 5 years. Four patients had multiple pituitary hormone deficiencies. The main characteristics of the patients are given in Table 1. In case 1, magnetic resonance imaging (MRI) results were normal at admission, but 6 months later, a pineal GCT was detected. While 2 patients had only pineal and 1 patient had only suprasellar lesion, 2 patients had a bifocal tumor (suprasellar and pineal) (Figure 1). Pathological examination demonstrated germinoma in 3 and dysgerminoma in 1 case.

All cases underwent appropriate treatment according to the decision of the multidisciplinary team. On the follow-up, 3 cases were in a good condition with appropriate hormone replacement therapy, but 2 died because of intercurrent complications.

Ankara University Ethics Committee approved the study by approval number: 2021000035.

GHTs are often present by hypophysial dysfunctions, especially CDI, and may lead to diagnosis when investigating the causes of pituitary dysfunction. The earliest sign of hypophysial dysfunction in our cases was CDI. As they can be slow-growing tumors, an obvious mass lesion may develop long after the first symptom. Thus, they may not be detected in the initial screening of CDI cases as seen in our 4 cases. Patients diagnosed with idiopathic CDI should be followed up carefully by close cranial MRI follow-up (in 3-6 month intervals).

There are difficulties for the final diagnosis of GHTs, mainly including the technical aspects of biopsy. If the tumor is located in critical vital areas, it can even be life-threatening, such as in 1 case. Cunliffe et al reported that, particularly, in patients with dense vascular structure, a biopsy could not be successful.
|                   | Case 1          | Case 2          | Case 3          | Case 4          | Case 5          |
|-------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Age of admission (year)** | 8.7             | 14.2            | 13.4            | 14.6            | 14.8            |
| **Admission symptoms** | Poliuria, polydipsia, ptosis in the left eye | Poliuria, polydipsia, headache, bilateral limited outward gaze, and nausea | Poliuria, polydipsia, headache, decreased eyesight, drowsiness, and vomiting | Poliuria, polydipsia, decreasing of vision, headache, nausea | Poliuria, polydipsia, headache, diplopia, and nausea. Operated hydrocephaly due to aquaductal stenosis 6 months before of admission |
| **Height SDS on admission** | 0.01            | 0.8             | −1.17           | 1.84            | −2.2            |
| **Neurological examinations** | Normal          | Normal          | Normal          | Normal          | Normal          |
| **AFP levels** (normal levels for serum: serum: 0–7 ng/mL, for CSF: 0–1 ng/mL) | Serum: 0.02 CSF: − | Serum: 1.73 CSF: 0.3 | Serum: 1.5 CSF: 1.2 | Serum: 1.49 CSF: 0.2 | Serum: 5.6 CSF: 0.2 |
| **hCG levels** (normal levels for serum and CSF: 0–2 mIU/mL) | Serum: 2.9 CSF: − | Serum: 4.4 CSF: 4.2 | Serum: 6.8 CSF: 9.7 | Serum: 3.96 CSF: − | Serum: 1.48 CSF: 2.21 |
| **Hypophyseal dysfunction** | CDI             | CDI, TSH deficiency, ACTH deficiency, gonadotropin deficiency | CDI, TSH deficiency, gonadotropin deficiency (diagnosed during follow-up), GH deficiency | CDI, TSH deficiency, high prolactin | CDI, TSH deficiency, gonadotropin deficiency, GH deficiency |
| **Duration of symptoms related to CDI before tumor diagnosis** | 9 months | 2.5 years | 5 years | 3 months | 2 years |
| **Previous radiological imaging before diagnosis** | Normal | Normal | Normal | Not done | Hydrocephaly due to aquaductal stenosis |
| **Diagnostic radiological imaging** | Pineal lesion (16 × 9 mm) | Pituirary nodular lesion (33 × 22 mm) | Suprasellar (38 × 38 × 30 mm) and pineal (121 × 9 mm) lesions | Suprasellar mass (14 × 12 × 12 mm) and solid lesion at pineal region (13 × 12 × 11 mm) | Pineal lesion (20 × 14 mm) |
| **Pathological findings** | Germinoma | First biopsy: lymphocytic hypophysitis Second biopsy: Germinoma | First biopsy: granulomatous hypophysitis Second biopsy could not be done | Germinoma | Dysgerminoma |
| **Treatment** | Gamma knife+RT | Chemotherapy+RT | RT | Chemotherapy+RT | Chemotherapy |
| **Follow-up duration (year)** | 3.3             | 3.8             | 3.1             | 0.75            | 0.9             |
| **Last examination** | Good in health with CDI | Good in health with multiple hypophyseal hormone deficiency | Good in health with multiple hypophyseal hormone deficiency | Died during treatment due to neutropenic sepsis | Died during treatment due to adverse effect of chemotherapy |

CDI, central diabetes insipidus; TSH, thyroid-stimulating hormone; ACTH, adrenocorticotropic hormone; GH, growth hormone; CSF, cerebrospinal fluid; RT, radiotherapy.
One of the most important factors that make the diagnosis of germinomas difficult is that it can cause hypophysitis reaction and be confused with hypophysitis in pathological evaluation. Intracranial germinomas are highly immunogenic tumors and frequently contain a strong peri-tumoral immune response that can invade the surrounding tissue. Secondary hypophysitis was usually LH (82%) and occasionally GH (18%). Therefore, patients thought to have CDI due to primary hypophysitis should be rigorously screened for an underlying intracranial germinoma. The diagnosis of germinoma should be considered in the differential diagnosis, especially in cases with intracranial bifocal lesions that do not respond to hypophysitis treatment.

Bifocal (pineal-suprasellar) intracranial GCTs may rarely occur in childhood. In all GCTs, pineal-suprasellar synchrony is around 5%–27%. With the use of advanced radiological imaging methods, the frequency of diagnosis of bifocal germinomas is increasing. Bifocal ones are usually seen in children and young adults and peak around the age of 10–12 years. Symptoms and clinical picture may be variable depending on the location and size of the tumor, and the age of the patient.

Diagnosis and treatment of GCTs with pituitary dysfunction is complicated and should be individualized according to tumor characteristics. A multidisciplinary team approach that includes pediatric endocrinology, neurosurgery, pediatric oncology, and radiation oncology is essential.

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