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Hypophyseal Dysfunction and Difficulties in Management of Pediatric Intracranial Germ Cell Tumors

Mehmet İsakoca[1], Gökmen Kahiloğulları[2], Zeynep Şıklar[1], Tuğba Kontbay[1], Emel Ünal[3], Nurdan Taçyıldız[3], Handan Dinçaslan[3], Merih Berberoğlu[1]

[1]Department of Pediatric Endocrinology, Ankara University School of Medicine, Ankara, Turkey
[2]Department of Neurosurgery, Ankara University School of Medicine, Ankara, Turkey
[3]Department of Pediatric Oncology, Ankara University School of Medicine, Ankara, Turkey

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.[1,2] Intracranial GCTs are difficult to be differentiated from various neoplastic or inflammatory diseases due to similar clinical, radiological, and even pathological findings.[3-5]

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. The first biopsies of pituitary lesions of case 2 and case 3 were reported as "lymphocytic hypophysitis (LH)" and "granulomatous hypophysitis (GH)," respectively. These patients did not respond to treatment for hypophysitis. A second biopsy could not be performed due to the life-threatening condition in case 3. Radiotherapy was given considering the clinical, laboratory, and radiological findings and the diagnosis of Germ cell tumor (GCT), and the tumor regressed successfully.

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 hypophyseal dysfunctions, especially CDI, and may lead to diagnosis when investigating the causes of pituitary dysfunction. The earliest sign of hypophyseal dysfunction in our cases was CDI. As they can be slow-growing tumors, an obvious mass lesion may develop long after the first symptom.[3] 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).[1,6,7]
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[8] reported that, particularly, in patients with dense vascular structure, a biopsy could not be successful.

Corresponding author:
Zeynep Şıklar
✉zeynepsklr@gmail.com
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Table 1. Characteristics of Cases

	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	Polyuria, polydipsia, decreasing of vision, headache, nausea	Polyuria, polydipsia, haedache, diplopia, and nausea. Operated hydrocephaly due to aquaductal stenosis 6 months before of admission
Height SDS on admisssion	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 CFS: 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 CFS: 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 symptomes 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)	Pituitary 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 multipl hypophyseal hormon deficiency	Good in health with multipl hypophyseal hormon 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.

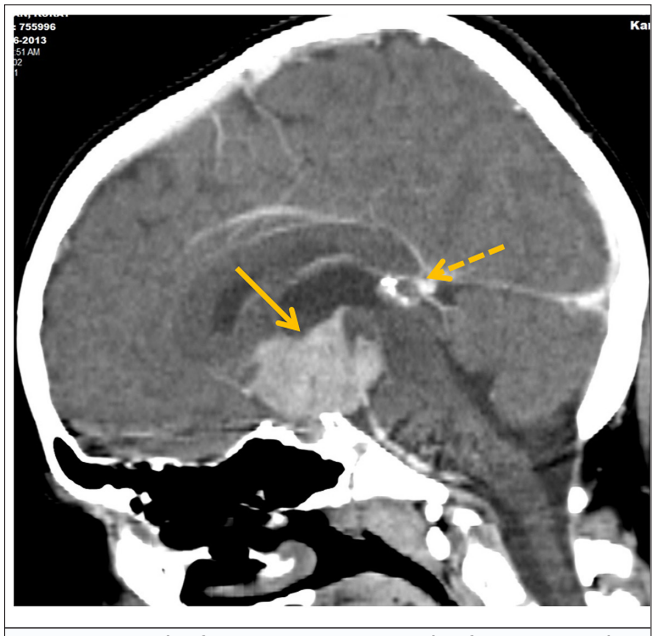

Figure 1. Sagittal reformat contrast CT study of case 3 reveals a heterogeneous dense contrast mass (line arrow) with cystic component, which fills the sellar cavity and extends into the suprasellar cavity, interpeduncular cisterna, the third ventricle. In addition, peripheral contrasting lesion (dotted arrow) contains peripheral calcification foci in the pineal area.

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.[4] 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%).[5] 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%.[3,8] 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.[9] 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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REFERENCES

1. Di Iorgi N, Napoli F, Allegri AE, et al. Diabetes insipidus—diagnosis and management. *Horm Res Paediatr*. 2012;77(2):69-84. [CrossRef]
2. Sethi RV, Marino R, Niemierko A, Tarbell NJ, Yock TI, MacDonald SM. Delayed diagnosis in children with intracranial germ cell tumors. *J Pediatr*. 2013;163(5):1448-1453. [CrossRef]
3. Hayden J, Murray MJ, Bartels U, et al. Symptom interval and treatment burden for patients with malignant central nervous system germ cell tumours. *Arch Dis Child*. 2020;105(3):247-252. [CrossRef]
4. Guzzo MF, Bueno CB, Amancio TT, et al. An intrasellar germinoma with normal tumor marker concentrations mimicking primary lymphocytic hypophysitis. *Arq Bras Endocrinol Metabolol*. 2013;57(7):566-570. [CrossRef]
5. Pal R, Rai A, Vaiphei K, et al. Intracranial germinoma masquerading as secondary granulomatous hypophysitis: a case report and review of literature. *Neuroendocrinology*. 2020;110(5):422-429. [CrossRef]
6. Oishi M, Morii K, Okazaki H, Tamura T, Tanaka R. Neuro hypophyseal germinoma traced from its earliest stage via magnetic resonance imaging: case report. *Surg Neurol*. 2001;56(4):236-241. [CrossRef]
7. Maghnie M, Cosi G, Genovese E, et al. Central diabetes insipidus in children and young adults. *N Engl J Med*. 2000;343(14):998-1007. [CrossRef]
8. Cunliffe CH, Fischer I, Karajannis M, et al. Synchronous mixed germcell tumor of the pineal gland and suprasellar region with a predominant angiomatous component: a diagnostic challenge. *J Neurooncol*. 2009;93(2):269-274. [CrossRef]
9. Hadjikoutis S, Hughes T. Germinoma with synchronous involvement of the pineal gland and the suprasellar region: a treatable cause of visual failure in a young adult. *Eye (Lond)*. 2004;18(5):525-526. [CrossRef]