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REVIEW ARTICLE

Intracranial germ cell tumours. A review with special reference to endocrine manifestations

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Abstract

Epidemiology. Intracranial germ cell tumours (icGCTs) represent 3–15% of primary paediatric intracranial neoplasms with a considerable geographical variation in incidence. Ninety percent of patients diagnosed with icGCTs are under 20 years of age. *Pathology.* Histologic characteristics and investigation of the tumour markers β-human chorionic gonadotropin (β-hCG) and alpha-fetoprotein (AFP) help define the different categories of icGCTs. The tumours are divided into two major groups called germinomas and non-germinomatous GCTs (NGGCTs). *Clinical presentation.* The clinical symptoms depend on the size and location of tumour in the brain, which is most commonly in the pineal or suprasellar region. Pineal GCTs often present with neurological symptoms because of their tendency to cause increased intracranial pressure. Suprasellar GCTs are often accompanied by endocrine abnormalities such as diabetes insipidus (DI), growth retardation and precocious or delayed puberty. *Diagnosis.* A combination of clinical findings, endocrine and tumour marker evaluation, spinal fluid cytology, magnetic resonance imaging (MRI) and biopsy helps verifying the diagnosis of an icGCT. A summary of published data (n = 97) revealed that >90% of patients at diagnosis had at least one endocrine abnormality, DI being the most common (>80%). *Treatment.* Classification of tumour is important for choice of treatment and for prognosis. A combination of chemotherapy and radiotherapy is often used, since most icGCTs have a great sensitivity to these treatment modalities. *Conclusion.* Endocrine symptoms are very frequently appearing in patients with icGCTs and they can present long before neuroimaging verification of tumour is possible. It is of the outmost importance to have the diagnosis of icGCTs in mind when children, adolescents and young adults are presenting with endocrine irregularities, because most icGCTs are very sensitive to radiotherapy and chemotherapy, and early onset of treatment is important in order to minimize morbidity and mortality.

Intracranial germ cell tumours (icGCTs) are rare neoplasms primarily affecting children and adolescents. They comprise a variety of histologically distinct tumours. Based on characteristics of the histological components they have classically been divided into two main groups called germinomas and non-germinomatous germ cell tumours (NGGCTs). Germinomas account for two thirds of cases. Extracranial GCTs appear most often in the gonads. The gonadal counterparts to intracranial germinomas are termed dysgerminomas when located in the ovaries and seminomas when in the testes. Extragonadal GCT typically arise in midline locations such as the mediastinum, retroperitoneum and the pineal and suprasellar regions of the brain.

Intracranial GCTs present with clinical features dependent of location and size of tumour. Symptoms most often arise from effects on optical structures, increased intracranial pressure and endocrine abnormalities, especially diabetes insipidus (DI). In some cases neurologic and endocrine disturbances appear long before radiological evidence of tumour can be demonstrated. The clinical findings and increased concentrations of the tumour markers β-human chorionic gonadotropin (β-hCG) and alpha-fetoprotein (AFP) in serum and/or cerebrospinal fluid (CSF) indicate the presence of an intracranial germ cell tumour.

There is considerable controversy concerning the treatment of icGCTs. Germinomas are more sensitive to radiotherapy and chemotherapy than NGGCTs. The histological diagnosis is consequently important for planning of treatment. The treatment is given with curative intent and should be delivered so that late effects related to treatment are minimised. The endocrine dysfunctions occasionally persist after treatment

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of tumour, which can be due to effects of direct tumour growth or side effects to radiotherapy and surgery. It is therefore important to restrict the extent of surgery and limit dose and volume of radiotherapy to an acceptable minimum. Some patients will be dependent on permanent hormone substitution subsequently.

Epidemiology

The incidence of primary intracranial germ cell tumours (icGCTs) varies considerably globally. According to Western literature icGCTs encompass 0.3–0.5% of all primary intracranial neoplasms and approximately 3% of primary malignant paediatric brain tumours. Series from Japan and Taiwan indicate that these tumours are far more common in Asia, where icGCTs make up 2–5% of all primary intracranial neoplasms and account for up to 15% of primary paediatric intracranial neoplasms [1].

Ninety percent of patients with icGCTs present with symptoms before the age of 20 years [2]. Sixty-five percent of tumours occur in the second decade of life (11–20 years). The peak incidence is around 10–12 years of age [3,4]. Intracranial germinomas appear mainly in the pineal and suprasellar regions. Less common locations are the basal ganglia, ventricles, thalamus, medulla oblongata or the cerebral hemispheres [1].

Intracranial GCTs affect males more frequently than females with an estimated male-to-female ratio of 2.5:1. Incidences by tumour location have specific trends based on gender. Pineal germinomas show male predominance with a male-to-female ratio of 3:1, whereas suprasellar germinomas tend to affect females more often than males [4].

Intracranial GCTs are found as both solitary and multiple lesions. When the pineal and suprasellar region are affected synchronously the term bifocal lesion is used. This phenomenon is seen at time of diagnosis in 5–10% of patients with icGCTs and is more frequently observed in males than females [2,5].

Pathology

Etiology

Different theories suggest the origin of germ cell tumours. Teilum's theory proposes, that extragonadal GCTs arise from a totipotent primordial germ cell that has migrated deviantly during embryonic development. The ectopic germ cells evade apoptosis and subsequently undergo neoplastic transformation [2,6].

Classification

The World Health Organization (WHO) has proposed a classification system for central nervous system (CNS) germ cell tumours that divides them into two major groups; germinomas and non-germinomatous germ cell tumours (NGGCTs). The classification system is based on the histological characteristics of the tumours, the presence or absence of tumour markers β-hCG and AFP on the neoplastic cell surface, in the serum and/or CSF.

The germinoma category includes germinoma with a syncytiotrophoblastic component, which secretes β-hCG, and pure germinoma that does not secrete tumour markers [2]. The most frequent subtype of icGCTs is pure germinoma. This type accounts for 60% of all cases [5].

The NGGCT category is divided into embryonal carcinoma, endodermal sinus tumours (yolk sac tumours), choriocarcinoma, teratoma and mixed germ cell tumour. Teratomas are further divided into malignant teratomas and benign mature and immature teratomas. The mixed tumours consist of more than one type of histology [2,7].

Clinical presentation

The display of initial symptoms depends upon localization and size of tumour. Lesions in the pineal region often obstruct the cerebral aqueduct causing obstructive hydrocephalus. This gives rise to symptoms of increased intracranial pressure such as headache, vomiting and diplopia. To relieve these symptoms a shunt placement or ventriculostomy is often required. Also frequently seen at presentation of a pineal GCT is Parinaud's syndrome. This phenomenon is caused by involvement of midbrain structures adjacent to the pineal GCT and is characterised by vertical gaze palsy, nystagmus on convergence and pupillary dilation with poor reactiveness to light. Somnolence, ataxia, seizures and behavioural changes can also be seen in connection with pineal GCT.

Patients with GCTs in the suprasellar region typically present with endocrinopathies and visual disturbances. The dysfunction of the hypothalamic-pituitary axis gives rise to symptoms such as DI, growth retardation, precocious puberty or delayed sexual development and menstrual irregularities. Different mechanisms result in the development of precocious puberty in the two sexes. Precocious puberty is defined as development of secondary sex characteristics before the age of nine years in males and before seven years in females. The high testosterone level in males inducing early onset of puberty, can be due to increased β-hCG. Development of precocious puberty in females is more complicated, since this requires a rise in LH and FSH in addition to an increase in β-hCG. For this reason, precocious puberty caused by intracranial tumours is far more common in males than females.

The ophthalmic abnormalities are due to compression of visual pathways and involve deficits in visual acuity, strabismus, diplopia and bitemporal heminopsia. Patients with bifocal disease tend to present with symptoms characteristic of suprasellar mass lesion [2,4,7,8].

Endocrine abnormalities often appear prior to clinical neurological findings or radiological manifestations. Especially DI can precede all other abnormalities and it is thus often an early clinical manifestation of a suprasellar GCT. DI is often the first appearing symptom, but in some cases it develops during the course of the disease.

Endocrinopathies in patients with only pineal tumour are less common. Lin et al. described a case in which a patient suffered from DI for three years before the tumour was radiologically detectable [9,10]. This indicates a rather low sensitivity of the radiological imaging.

Magnetic resonance imaging (MRI) scan is mandatory in cases with unclarified central DI and other endocrinopathies [11]. Furthermore, tests of anterior pituitary function and measurement of tumour markers should be carried out at regular intervals in case of idiopathic DI, because these investigation modalities can be more sensitive than scans [12]. Ten to 15 percent of patients experience metastatic involvement of the medulla spinalis. Systemic metastases originating from icGCTs are very rare. Haematogenous spread to the lungs, liver, spine and rarely bone has been reported [3,4].

Summary of findings from the literature with special reference to endocrine parameters

Table I is a survey of the characteristics of 97 patients diagnosed with intracranial GCT compiled from 16 studies. There was an approximately equal distribution of sexes in the group, with 40 females versus 57 males. Patients were categorised as children if they were diagnosed before the age of 15 and as adults if they were 15 or older at the time of diagnosis. Seventy-one patients constituted the group of children and the remaining 26 were adults. The anatomical site was suprasellar in 43 cases, pineal in 13 and bifocal in seven. The tumour was located intrasellarly in four patients, multifocal in 10, basal-ganglia in five and in the pituitary region in two. Six patients had only pituitary stalk thickening indicating tumour presence radiologically. Two scans were normal and two were inconclusive.

Diabetes insipidus was diagnosed in 78 of 95 patients investigated. The cortisol level in serum was reduced in 44 of 76 patients. Nine of 25 patients had a reduced level of TSH, one of 25 had an increased level of TSH and 18 of 43 patients had a reduced level of thyroxine. The sexual hormones tended to be reduced if abnormal. Three of 26 patients had a reduced LH level, whereas two of 26 had an elevated level of LH. FSH was reduced in 11 of 26 patients. LH and FSH were reduced in 19 of 24 patients. One patient had an increased testosterone level and one had a reduced level. Estrogene or testosterone was reduced in three of 22 patients. Serum prolactine was higher than normal in 33 of 41 patients. The level of growth hormone was below normal in 51 of 78 cases. Four of 13 had a β-hCG value higher than normal in CSF. Thirteen of 51 had an elevated level of β-hCG measured in serum. Ten of 10 had a normal AFP value in the CSF and four of 37 were registered with an AFP value above the normal limit.

Diagnosis

When the suspicion of an intracranial GCT arises, the confirmation of the diagnosis depends on clinical and paraclinical findings. A thorough general clinical examination along with neurological and visual examinations should be carried out [2]. Endocrine dysfunction related to the hypothalamic/pituitary axis in children and young adults should give rise to suspicion of intracranial tumour. Especially DI is often an early clinical manifestation of a suprasellar GCT. When elevated serum titers of the tumour markers β-hCG and AFP are found, it could indicate the presence of a gonadal or extragonadal germinoma in the body. Low levels of β-hCG in serum can be detected in a variety of different malignancies. If the CSF contains β-hCG and/or AFP it indicates a tumour secreting these markers somewhere in the CNS.

Neuroimaging assessment is used to confirm the presence of an intracranial GCT. It is important though to remember that a time lag between the appearance of symptoms and radiological detection occasionally occur. MRI is the most reliable tool for radiological detection of intracranial GCTs [7,9,13]. It has been reported that one of the first abnormal findings on MRI scan of patients with intracranial GCT is isolated thickening of the pituitary stalk [14]. Since the radiographic characteristics are similar in the various types of GCTs, it is not possible to differentiate the specific histological diagnosis of the tumour based on radiological examination alone.

A tumour biopsy is normally mandatory in order to establish the correct diagnosis. Exceptions can be made in cases where significant elevations of tumour markers in CSF and/or serum are documented. Pure germinomas secrete very little or no tumour markers, contrary to NGGCTs that often present with elevated tumour marker levels. Spinal fluid cytology may be helpful in detecting craniospinal spread. Since intracranial GCTs have a propensity to disseminate

Table I. Summary of 97 patients.

Reference number	No. of patients	F	M	Child*	Adult	Anatomic site	DI	Cortisol	Thyroid hormones	Sex hormones	Prolactine	Growth hormone	ß-hCG spinal	ß-hCG serum	AFP spinal	AFP serum
5	1	–	1	–	1	1 MF	1/1	↓	→TSH →Thyr	↓LH ↓FSH	↑	–	→	→	→	→
7	1	1	–	1	–	1 B	1/1	↓	→TSH	–	↑	–	→	→	→	→
8	1	–	1	1	–	1 IS	1/1	–	↓TSH →Thyr	↑Test ↑LH →FSH	↑	→	–	↑	–	↑
9	12	5	7	12		3 P 6 SS 2 B 1 BG	8/12	–	–	–	–	–	–	–	–	–
11	1	–	1	–	1	1 B	1/1	→	→TSH	→LH ↓FSH	↑	→	–	↑	–	–
12	1	–	1	1		1 P	1/1	→	→TSH	→FSH + LH	→	→	–	↑		→
13	14	4	10	13	1	4 P 6 SS 1 IS 3 B	14/14	↓9/13	–	↑LH 1/14 ↓FSH 1/14	–	↓11/13	–	↑3/10	–	↑2/10
14	3	2	1	3	–	2 PR 1 TS	2/3	↓1/2	↓Thyr 2/3	–	–	–	→3/3	–	–	–
16	7	1	6	1	6	3 P 2 SS 1 MF 1 TS	6/6	↓4/6	↓TSH 2/7 ↑TSH 1/7	↓FSH 6/7 ↓LH 4/7 ↑LH 1/7	↑4/6	→7/7	–	↑4/7	–	↑1/7
17	1	1	–	–	1	1 IS	–	→	↓Thyr	↓LH ↓FSH	↑	–	→	↑	→	→
19	17	8	9	9	8	17 SS	15/17	↓9/12	↓TSH 6/13	↓LH + FSH 11/15	↑12/14	↓14/17	–	↑6/13	–	–
21	1	–	1	–	1	1 IS + P	1/1	↓	–	↓Test ↓LH ↓FSH	↑	↓	↑	–	→	–
22	6	5	1	5	1	4 TS 2 NS	6/6	↓3/6	→Thyr 6/6	–	↑4/6	↓5/6	↑3/6	→6/6	→6/6	→6/6
23	8	3	5	4	4	4 SS 2 IS + SS 2 IC	7/8	↓8/8	↓Thyr 6/8	↓LH + FSH 8/8	↑7/8	↓8/8	–	↑1/8	–	→8/8
24	22	10	12	21	1	8 SS 2 P 4 BG 8 MF	13/22	↓6/22	↓Thyr 8/22	↓Est or Test 3/22	–	↓11/22	–	–	–	–
25	1	–	1	–	1	1 IS	1/1	↓	↓Thyr	–	–	↓	–	→	–	→
Total	97	40	57	71	26		78/95	↓44/76	↓TSH 9/25 ↑TSH 1/25 ↓Thyr 18/43	↓LH 3/26 ↑LH 2/26 ↓FSH 11/26 ↓LH + FSH 19/24 ↓Test 1/2 ↑Test 1/2 ↓Est or Test 3/22	↑33/41	↓51/78	↑4/13	↑13/51	→10/10	↑4/37

–, not informed; F, Female; M, Male; P, pineal; SS, suprasellar; IS, intrasellar; B, bifocal; MF, multifocal; BG, basal ganglia; PS, pineal stalk; TS, thick stalk; PR, pituitary region; IC, inconclusive; NS, normal scan; Thyr, thyroxine; Test, testosterone; Est, estrogene.

*< 15 years of age at time of diagnosis.

throughout the neuroaxis it is important to make an extensive evaluation including an MRI of brain and spine, CSF cytology and measurement of tumour markers [2,4].

Treatment

There is no complete consensus on the optimal management of patients suffering from intracranial GCTs. Choice of treatment and prognosis differs depending on the existing type of icGCT. Therefore, it is mandatory to clarify the histopathological diagnosis.

Efficacy of radiotherapy depends on the type of tumour. Intracranial germinomas are potentially curable with radiotherapy treatment with a reported 5-year survival rate above 90%. NGGCTs are less radiosensitive and they have a worse prognosis with a reported 5-year overall survival of 30–50% and a high incidence of relapse. The optimal dose and radiation field have not yet been defined. The long-term complications on neurocognitive and endocrine development resulting from radiotherapy, has made it desirable to reduce radiation exposure but without compromising mortality. Germ cell tumours are very sensitive to cis-platin based chemotherapy. A combination of radiotherapy and chemotherapy is often used. By combining the two modalities it is possible to increase the curative effect, to reduce radiation dose and thereby the late effects [2,15,16].

There is a general agreement that patients with metastatic intracranial germinoma require craniospinal irradiation (CSI). Patients with germinoma have traditionally received prophylactic radiotherapy to the craniospinal axis as part of primary treatment. But studies have documented that CSI is not necessary for localised germinomas [2,7]. In case of elevated levels of tumour markers in the CSF it is most likely a sign of dissemination and CSI is necessary [26]. AFP and β-hCG are useful as markers of treatment efficacy, because they indicate tumour's response to treatment. Changes in tumour markers are more sensitive than changes in images and are used in follow-up of patients [8,17].

A treatment strategy has been elaborated based on a French study from 1999 with chemotherapy and radiotherapy treatment, and a German study with primary chemotherapy (two series) followed by surgery and radiotherapy. These guidelines for treatment of patients with malignant GCT imply the following:

1) Patients with tumour diameter of less than 2 cm, without raised tumour markers in CSF and without medullary metastases as evidenced by MRI are given local irradiation (30 Gy in 15 fractions) towards the primary tumour.
2) Patients who do not comply with the criterias mentioned above, are primarily treated with chemotherapy, i.e. two series of cisplatinum + etoposide + bleomycin (PEB), followed by evaluation by means of MRI. If the tumour responds to this treatment, two additional series of PEB is given, followed by craniospinal irradiation. If the tumour does not respond to the two first series of PEB, the two next series of PEB are omitted and the patient is treated with craniospinal irradiation.
3) Residual tumour should be removed if possible, applying the same principle as with other germ cell tumours [18].

Cases presenting with obstructive hydrocephalus should undergo endoscopic third ventriculostomy (ETV). During the ETV procedure, histological samples of tumour can be obtained as well as CSF samples for cytology and tumour marker analyses. ETV is preferred ahead of ventriculoperitoneal shunting to avoid the risk of peritoneal seeding of tumour cells [3].

Infiltrative growth or mass effect of tumour can cause dysfunction of the pituitary gland, which expresses itself by the endocrine abnormalities. Sometimes this influence is transient and the pituitary gland regains its ability to secrete hormones after treatment. In other cases, the endocrine dysfunction is permanent. Surgery and radiotherapy can damage pituitary cells, reflecting the clinical observation that pre-existing hypopituitarism worsens after treatment. Radiotherapy can occasionally induce slowly progressive deterioration of residual pituitary function.

Diabetes insipidus often persists after treatment of tumour and the patient continues to need a vasopressin analogue. It has been observed, that even though the children tend to increase in height, they grow poorly. Many of the younger patients are receiving growth hormone (GH) substitution for this reason, and because the development of secondary sex characteristics tend to stop developing if GH is not given. Thus several patients need hormone substitution of some sort [16,19].

Treatment of relapsed or residual intracranial GCT

Relapsing or residual malignant disease is treated using the same principles as for other germinative tumours, i.e. systemic treatment with taxan-containing regiments or high-dose chemotherapy with infusion of peripheral stem cells. The prognosis for patients with relapsing disease is rather poor [20].

Conclusion

Though intracranial GCTs are rare, it is important for physicians, especially paediatricians, to be familiar with this disease, as it is potentially curable. Lack of specific clinical symptoms and an interval between initial symptoms and radiological detection contribute to the diagnostic difficulties.

Our summary of 97 patients diagnosed with icGCT shows, that some kind of endocrine abnormality is nearly always appearing in the patients. DI is remarkably frequent in patients with icGCT. In case of idiopathic DI, it is strongly advised to do follow-up at regular intervals, since icGCT might appear later. This follow-up involves tests of pituitary function, neurological examinations and screening blood and CSF of tumour markers. These measurements are more sensitive than radiological examination and they can help establish tumour presence earlier than MRI.

Blood levels of cortisol, sexual hormones, TSH and thyroxine are often reduced but can present as elevated as well. Mechanical pressure or infiltrative lesions excerted by icGCTs are thought to cause the lowered hormone production and secretion.

Dopamine released from hypothalamus has an inhibitory effect on prolactine secretion. Reduced dopamine secretion causes increased secretion of prolactine, which explains the increased level of prolactine found in 33 of 41 investigated patients.

Precocious puberty is only seen in a very few patients and mainly in boys as a result of elevated β-hCG level produced by tumour. The onset of puberty is more complex in girls involving gonadotrophins as well.

Growth hormone level was reduced in 54 of 81 cases (Table I). Just like DI, retarded growth can be a very early sign of a GCT in the suprasellar region. Follow-up should be carried out in paediatric patients with a history of growth retardation [14].

None of the different endocrine disturbances are patognomic for icGCT. If endocrine abnormality appears clinically or from laboratory results, perhaps together with the presence of neurological symptoms, an intracranial GCT should be considered. If no tumour is identified with MRI, follow-up is strongly recommended. Early diagnosing is important to minimise late effects from tumour growth and treatment. Late effects include hormone disturbances that sometimes persist throughout life.

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