Germ cell tumours in children and adolescents

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Abstract

Germ cell tumours (GCTs) comprise a heterogeneous group of tumours believed to arise from the totipotent primordial germ cell. While uncommon, they may present at any age from in-utero to young adulthood. Prognosis is generally good and considering them in the differential diagnosis of midline as well as gonadal masses may prevent diagnostic delay and/or escalation of potentially harmful treatment. In childhood, approximately 50% are gonadal and 50% extragonadal (20% intracranial/30% extracranial). Clinical presentation relates to mass effect at tumour site. Teratomas account for 50% of paediatric GCTs and, whilst considered benign, may recur if not completely excised. Malignant GCTs often secrete the tumour markers alpha-fetoprotein and human chorionic gonadotrophin, which may help in diagnosis and follow-up. Outcomes are generally good with >90% five-year overall survival. Management involves complete surgical resection for teratomas and non-metastatic gonadal tumours. In the UK, chemotherapy is reserved for stage 2–4 extracranial malignant GCTs. Intracranial tumours typically occur in the midline in the pineal and/or suprasellar regions. Intracranial germinomas are cured in >90% cases with radiotherapy or combined chemo-radiotherapy. About two-thirds of non-germinomatous intracranial tumours are cured with combined chemo-radiotherapy. Current issues relating to the diagnosis and management of teenagers and young adults with GCTs are highlighted.

Keywords children; extracranial; extragonadal; germ cell tumour; gonadal; intracranial; primordial germ cell; teenagers and young adults with cancer; tumour biology; tumour marker

Introduction

GCTs are a heterogeneous group of benign and malignant tumours, and usually occur in gonadal and midline extragonadal sites. Being pluripotent, they can form all embryonal (ectoderm, mesoderm and endoderm) and extra-embryonal (yolk sac and placental) tissues. The distribution of GCTs varies with regard to age, site and histopathology. See Table 1 for classification and common presentation of GCTs in children.

Epidemiology

GCTs may present from birth, through childhood and adolescence to (rarely) old age. They are rare with an annual incidence of approximately 0.5/100000 in children under 15 years, accounting for 2–4% of childhood tumours. They have a bimodal age distribution with a small peak in infants less than 3 years and a larger one in adolescence, with extracranial GCTs accounting for 14% of all cancers in the 15 to 19 age group (see Figure 1).

The aetiology of GCTs is largely unknown, but there is a well-established relationship between sex-chromosomal abnormalities and GCTs. People with 46, XY and 45, X/46, XY gonadal dysgenesis have a 10%–50% risk of developing a gonadal germ cell tumour. In Klinefelter syndrome (47, XXY) there is an increased risk of developing mediastinal and, to a lesser extent, other extragonadal germ cell tumours. In females, there is an association of Turner syndrome and Swyer syndrome with ovarian GCTs. There is also an increased incidence of GCTs in children with sacral agenesis, aniridia- Wilms association, males with Russell-Silver Syndrome and Down Syndrome (testicular GCTs). GCTs are one of the few solid tumours occurring more commonly in children with Down Syndrome, in contrast to other solid tumours of childhood, which occur less frequently.

Pathology

The pathological classification is complex. Germinomas [also known as seminomas (testes), dysgerminomas (ovary)] remain in their undifferentiated state and have pathological features of undifferentiated germ cell epithelium. Yolk sac tumours (YST) and choriocarcinoma (CHC) have extra-embryonic differentiation while embryonal carcinoma (EC) is thought to undergo embryonic differentiation and consists of immature totipotent cells. Teratomas, both mature and immature arise as a result of somatic maturation and tissues may reflect all germ layers. Immaturity is defined by the extent of immature elements. There is a relationship between degree of immaturity and likelihood of relapse in teratomas, particularly after incomplete resection. Gonadoblastoma is a benign, but potentially premalignant condition associated with stromal components (i.e. streak ovary) in dysgenic gonads only in the presence of the Y chromosome (i.e. 46XY in female phenotype).

Histologically, GCTs in children often contain more than one sub-type, and treatment strategy should be tailored to the most aggressive sub-type present.

Tumour markers

The secretion of alpha-1-fetoprotein (AFP) and the β-subunit of human choriogonadotropin (β-hCG) by some GCTs is useful in aiding non-invasive diagnosis, monitoring of treatment response and early detection of relapse. AFP is normally secreted by embryonic tissues and is elevated in children with yolk sac tumours and embryonal carcinomas. β-hCG is secreted by choriocarcinoma and embryonal carcinoma. Some teratomas secrete AFP as they contain yolk sac elements.

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Common germ cell tumour sites. Demographics and clinical presentation

Tumour site	Percentage of GCT < 15 yrs	Age	Histology	Demographics	Common/unusual clinical	Genetic associations
Testes	25%	0—5 years	Teratoma YST		Painless mass	Undescended testes
		15—30 years	Non-seminoma (embryonal carcinoma)/mixed malignant GCTs Seminoma uncommon	Commoner in white than non-white males	Painless mass	Undescended testes Down syndrome Russel Silver Syndrome 46XY, 45X/46XY are at increased risk
Ovarian	25%	Median age 13 years	Dysgerminoma 24% YST 16% Teratoma 41% Embryonal carcinoma 6% Mixed malignant GCT 11%	Commoner in non-white than white females	Palpable abdominal mass & abdominal distension. Pain suggests torsion/ rupture Virilisation and menstrual changes in B-HCG secreting tumours Dysgerminoma: bilateral in up to 20%	Turners syndrome Swyer syndrome
Intracranial Pineal (60% of CNS GCTs) Suprasellar (30% of CNS GCTs)	20%	Median age	2/3 germinoma 1/3 NGGCT 5—10% bifocal	M:F 2:1 M:F 4—5:1 F: M 1—1.5:1	Raised ICP, Parinaud syndrome DI Raised ICP Hypopituitarism Visual disturbance Precocious puberty	
Basal ganglia/other Extragonadal Extracranial						
Sacrococcygeal	20%	Diagnosed from pre-natal into infancy	Mostly mature & immature teratoma with 9% incidence of YST. Higher (25% if diagnosed in infancy)	F: M ratio 3:1 Greater internal component if diagnosed in infancy	Antenatal USS Mass in sacral region. >80% diagnosed at <1month old Functional problems related to mass/ surgery effect in infants	Congenital anomalies in approx. 18%: musculoskeletal and CNS defects are most common
Other extragonadal Mediastinal (Usually anterior mediastinum)	10%	After 9 years Mean age 13 years	Teratoma & YST in young children All types in older children	M > F	Airway compromise/ SVC obstruction. Hormone disturbance less likely	47XXY at greatly increased risk and present earlier than with normal karyotype

Abbreviations: GCT, germ cell tumour; YSC, yolk sac tumour, *B*-HCG, beta-human chorionic gonadotrophin; NGGCT, Non-germinomatous GCT; M, male; F, female; USS, ultrasound scan; CNS, central nervous system; SVC, superior vena cava.

Table 1

Failure of tumour markers (TM) to fall appropriately or rise can be the first sign of the need for further investigation and treatment. Levels of AFP are elevated at birth (normal range: 7660—160069 kU/l) and fall slowly to adult levels between one and two years of age. As the normal range suggests levels are highly variable and single measurements can be misleading. Isolated elevated levels in children less than two years should be repeated and in an individual infant would be expected to fall

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