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Short Communication

Germ Cell Cancers in Adult Males are Associated with a History of Infantile Pyloric Stenosis

A.B. Hassan and G.M. Mead

Wessex Medical Oncology Unit, Royal South Hants Hospital, Brintons Terrace, Southampton SO9 4PE, U.K.

Germ cell cancers (GCT) are the most common cancers of young men and are curable in at least 90% of cases. A number of aetiological factors have been identified which predispose to the development of these cancers, such as cryptorchidism and hernia. We report the association of GCT with infantile pyloric stenosis (IPS). The case records from 542 adult males with germ cell cancer arising from any site were screened for a history of pyloric stenosis requiring surgical treatment. Nine cases were observed (expected number = 2.168; chi squared = 21.5 ($P < 0.001$), standardised ratio = 4.15; 95% confidence interval 1.9–7.88). The recognition of rare associations of germ cell tumours may lead to the identification of genetic and environmental factors involved in their aetiology. © **1997 Elsevier Science Ltd.**

Key words: germ cell cancer, pyloric stenosis

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INTRODUCTION

GERM CELL cancers (GCT) are the most common malignancy of men of 18–35 years of age. In the majority of cases, the gonads are the primary site. Testicular cancer is a model for curable metastatic malignancy. For example, 80–90% of patients with metastatic testicular teratoma are cured after cisplatin-based chemotherapy and surgical resection of residual masses [1]. Numerous studies have identified aetiological risk factors, such as cryptorchidism (there is an approximately 10 times greater risk of testicular cancer in such men), hernia and exercise. Rarer associations are with genitourinary, musculoskeletal, chromosomal and dermatological abnormalities [2]. In the majority of cases, however, tumours appear to arise in previously well young men without any apparent predisposition. This paper reports a new association of germ cell tumours presenting in patients with a history of infantile pyloric stenosis (IPS).

PATIENTS AND METHODS

The Wessex Medical Oncology Unit (WMOU) is a regional referral centre for GCT requiring either monitoring or chemotherapy treatment. Several cases of GCT followed in the clinic were found to have a history of IPS requiring surgical correction. This led to the screening of case records for a history of IPS requiring surgical treatment in male patients (>18 years) with germ cell tumours (including extra-gonadal primary sites) referred to this centre between 1985 and 1995. Testicular cancer data (all histologies; ICD9-186 OPCS 1989) were obtained from the Wessex Cancer Intelligence Unit and related to the WMOU cases.

RESULTS

A total of 542 records were screened and 9 cases with a history of IPS identified Table 1. All cases had biopsy proven germ cell tumours (eight testicular primary, one mediastinal primary) and were staged by standard means. Two of the cases of IPS were associated with a family history of this disorder. Three cases had testicular maldescent and inguinal hernia, known risk factors for testicular GCT. During the period of this study, the WMOU was referred a mean of 48% of the cases seen within the Wessex region. From the period 1985–1992, a mean of 95% of all cases of teratoma in Wessex region were managed by WMOU (not shown), suggesting that the majority of the cases seen outside the WMOU were either early stage seminoma requiring radiotherapy or cases referred elsewhere.

IPS has an average incidence of 3–5 cases per thousand live male births. The incidence of IPS requiring surgical correction in the Wessex region 30 years ago is not known. The current rate is 2/thousand live births (Mr D. Burge,

Correspondence to A.B. Hassan.
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Table 1. Cases of germ cell tumours with a history of infantile pyloric stenosis (IFS) requiring surgical treatment

Age (years)	Stage	Histopathology	Family history of IPS	Risk factors	Other conditions
38	I	Seminoma	—	IH	Duodenal ulceration
31	I	MTI	—	—	Ankylosing spondylitis
20	MED	YLK	—	—	—
27	I	MTU YLK	—	Maldescent	—
16	IM	MTI	+ father	—	—
23	I	MTU YLK	+ father	IH	—
35	I	MTU	—	—	—
19	IVB L3	MTI YLK	—	—	—
34	I	Mixed*	—	—	—

*Mixed seminoma, MTI and YLK.

MED, mediastinal primary; MTU, malignant teratoma undifferentiated; MTI, malignant teratoma intermediate; YLK, yolk sac; IH, inguinal hernia; IM, raised markers, but no clinical evidence of metastatic disease.

Department of Paediatric Surgery, Southampton General Hospital, U.K.). The indications for this operation are likely to vary between centres, and again it not known what the prevalence of this surgical procedure was 30 years ago. Furthermore, investigation of the HMSO tables of Surgical Operations and Procedures (Codes; G40.1/.3/.8) grossly underestimate the incidence of this procedure. We have, therefore, taken an average incidence of IPS requiring surgical correction as 4/thousand live male births. The expected number of cases of pyloric stenosis in the population examined would therefore be $\sim 4 \times 542/1000 = 2.168$. Using a chi-squared test on the sample population; $\chi^2 = 21.5$ ($P < 0.001$), standardised ratio = 4.15, 95% confidence interval, 1.9–7.88 (Confidence Interval Analysis software, BMJ 1991). If the sample population is restricted to WMOU cases more representative of the Wessex region, i.e. those with testicular teratoma (total cases = 338, index cases = 7), then the expected number of cases would be 1.35 and $\chi^2 = 23.6$ ($P < 0.001$).

These results suggest that male patients with GCT have at least a 4-fold increased incidence of previous surgical correction of IPS.

DISCUSSION

We have described nine cases of IPS who developed germ cell tumours in adult life. Is this a chance association? A significantly greater number of observed cases compared to those expected was found in our patient population (9 versus 2), with two cases associated with familial IPS. Although accurate estimates of the prevalence of surgical correction of IPS in the Wessex region are not known, there is no reason to believe that the prevalence in this region is significantly different to any other in the U.K. However, this is a single-centre analysis which requires confirmation, even though studies investigating social, behavioural and medical factors in cases of GCT have not yet found such an association [4].

What are the implications of this type of observation? The association of congenital abnormalities and malignancy is not new. The increased incidence of leukaemia in Down's syndrome and congenital immune deficiency syndromes is well described. A relationship between IPS and malignancy has, however, not been established. Berry and associates [5] reviewed 96 cases of childhood embryonic tumours including teratomas, neuroblastoma and nephroblastoma. Single cases of gonadal teratoma and neuroblastoma had IPS, but no congenital abnormalities were seen in cases of extragonadal teratomas (brain and mediastinum). Extensive record linkage studies in Atlanta, U.S.A. have recently suggested an association between IPS and childhood malignancy [6]. Records from a congenital defects registry (19373 cases) for Georgia were matched with the childhood cancer registry for that state (400 cases detected in children under 15 years). 3/532 cases of Down's syndrome developed acute leukaemia and, surprisingly, 4/746 children with IPS developed cancer, comprising 2 cases of acute leukaemias with single cases of neuroblastoma and glioblastoma. However, a similar study using data from Iowa, but with a shorter follow-up (8 years), failed to show a statistically significant association of childhood cancer with IPS [7]. As the average age of presentation of GCT is 30 years, prolonged follow-up in these studies would be required to identify any association between IPS and GCT. Longitudinal follow-up (>28 years) of 203 infants with IPS have failed to identify adult cases of germ cell tumours [10]. However, those infants with more severe clinical presentations of IPS appeared to be less fertile in adult life, suggesting that there may be a relationship between IPS and infertility, as there is for infertility and testicular germ cell tumours [2, 10]

Infantile hypertrophic pyloric stenosis usually occurs during the first few weeks of life and presents with projectile bile-free vomiting, dehydration and an abdominal mass (pyloric olive). The circular muscle of the pylorus becomes thickened and fails to relax, surgical correction is by incision of the hypertrophied muscle (Ramstedt's pyloromyotomy) and is curative. The incidence of IPS varies from 1 to 5 per 1000 live births with some geographical variation within the U.S.A., U.K. and Scandinavia [13]. Males are affected at least four times as often as females and the condition is less common in negro populations [13]. The cause of pyloric stenosis is unknown, but there is now evidence to suggest the depletion of nitrous oxide synthase occurs in the neuronal plexus within the pylorus [8]. Indeed, transgenic mice in whom the gene for nitrous oxide synthase is 'knocked out', appear to develop pyloric hypertrophy [9]. Analysis of kindreds suggests a multifactorial model of inheritance involving several genes yet to be identified.

What biological mechanism could account for the association between IPS and the subsequent development of germ cell cancers which we have identified? Firstly, we cannot rule out the possibility that GCT and IPS are simple manifestations of a generalised developmental disorder, without any specific link to a common genetic mutation. However, as with other tumours, the development of germ cell cancer may involve a multistep accumulation of genetic defects which also results in IPS. Little is known about the mutations that predispose to germ cell malignancy, even though a characteristic chromosomal abnormality [i(12p)], a mouse genetic model and a candidate region on human chromosome 4, have been identified [11, 12]. For example, it is not known whether defects exist in the nitric oxide pathways in GCT. Analysis of sib-pairs suggests that there may be an inherited predisposition to germ cell tumours, although candidate human genes have yet to be isolated [3, 12]. Unfortunately, in practice, the identification of genetic mutations in familial cancers has not automatically led to the detection of similar mutations in sporadic tumours. Further studies are required to identify the genetic and environmental factors involved in germ cell malignancy.

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