Seasonality of birth in children with diabetes in Europe: multicentre cohort study

P M Rothwell, S A Gutnikov, P A McKinney, E Schober, C Ionescu-Tirgoviste, A Neu for the European Diabetes Study Group

There is increasing evidence that environmental factors in early life, particularly viral infections, influence the risk of developing type 1 (insulin dependent) diabetes.[1] The high incidence of diabetes in the congenital rubella syndrome suggests that intrauterine infection may be important,[1] and the high incidence of enteroviral infection during pregnancy in the mothers of children who subsequently develop type 1 diabetes suggests that other viruses may also be involved.[2] Since most common viral infections are seasonal, if a significant proportion of cases of childhood diabetes were caused by intrauterine infection it might be expected that the pattern of dates of birth of affected individuals would be abnormal. We previously reported abnormal seasonality of birth in three large independent populations of children with type 1 diabetes in the United Kingdom,[3] and a similar pattern has since been reported in the Netherlands.[4] To determine whether regional variation in seasonal patterns of birth of children with diabetes might provide clues to the aetiology of the disease we studied 20 cohorts of children with diabetes from 16 European countries.

Subjects, methods, and results

We obtained data from population based incidence cohorts of children (0-14 years) who had type 1 diabetes diagnosed after 1989 and were registered with the European diabetes (EURODIAB) project. The dates of birth spanned 20 years (1974-94), and national monthly birth rates were obtained for this period. Data for this extended period were obtained for the previously reported British cohorts and duplicate cases removed. The pattern of births in each cohort was analysed separately. We adjusted for the seasonality of live births in the general population by constructing pseudocohorts of births based on the number of births by month in the period under study. Significance of seasonal trends was tested by the method of Walter and Elwood.[5]

Only the cohorts from Great Britain showed significant differences in the seasonality of birth between children with diabetes and the general population (table). There were no convincing seasonal trends elsewhere in Europe. Combining cohorts from Great Britain revealed a significant sinusoidal pattern of births with a peak in early summer, a trough in winter, and an amplitude of 20% (P = 0.006).

Seasonal pattern of dates of birth in cohorts of children with diabetes compared with that expected from national birth rates

Region	No of cases	χ^2 for seasonality of birth	P value
Great Britain:			
Scotland*	2408	8.9	0.01
Yorkshire*	1232	8.3	0.01
England and Wales*	1270	4.9	0.09
Oxford	758	5.2	0.07
Leicester	329	7.2	0.03
Total	5997	10.2	0.006
Austria	895	0.4	0.8
Czech Republic	1512	3.0	0.2
Denmark	296	3.3	0.2
Germany (Baden-Württemberg)	1303	1.4	0.5
Italy (Lazio)	471	1.9	0.4
Lithuania	486	0.8	0.6
Luxembourg	72	4.7	0.1
Malta	98	5.6	0.06
Northern Ireland	462	1.8	0.4
Poland	448	0.4	0.8
Romania	185	2.4	0.3
Italy (Sardinia)	886	1.7	0.4
Slovakia	889	3.0	0.2
Spain	914	1.6	0.5
Sweden (Stockholm)	520	0.3	0.8

*Cohorts contain patients reported previously.[3]

Comment

Although many of the cohorts from continental Europe were relatively small and had little power to exclude a modest degree of seasonality of birth, none of the cohorts showed any suggestion of abnormal seasonality. Moreover, aggregation of cases into three larger cohorts relating to areas of low, medium, and high incidence of diabetes (data not shown) also showed no abnormal patterns. Only the five cohorts in Great Britain showed any signs of a seasonal trend. The consistency of the finding in these studies and the significance of the overall seasonality suggest that the abnormal seasonal pattern of births is not due to chance, and it is difficult to conceive of any bias that might account for the observation.

If the abnormal seasonality of birth of children with diabetes in Great Britain, and that reported in the Netherlands,[4] is a consequence of infection in utero or in early infancy, then the infectious agent(s) responsible would be predicted to be less prevalent, to exhibit a less seasonal pattern of infection, or to be different, in most other parts of Europe. Further studies are required to determine whether abnormal seasonality of birth exists in childhood diabetes in other parts of the world and to identify likely causes. These should be multicentre collaborative studies to avoid bias due to the selective reporting of positive results by single centres.

Contributors: PMR planned the project, supervised analysis of data, wrote the paper, and is the study guarantor. SAG prepared and analysed data. PAMcK planned the project, established the protocol for data collection, and helped write the paper. ES, CI-T, and AN helped establish the study protocol, supervised the collection of data, and commented on drafts of the paper. The following EURODIAB collaborators (region) contributed data: C de Beaufort (Luxembourg); P Bingley (Oxford, UK); AC Burden (Leicester, UK); C Castell (Spain); O Cinek (Czech

Department of Clinical Neurology, University of Oxford, Oxford, OX2 6HE
P M Rothwell *consultant neurologist*
S A Gutnikov *research assistant*
Paediatric Epidemiology Group, University of Leeds, Leeds LS2 9LN
P A McKinney *senior research fellow*
Department of Paediatrics, University of Vienna, A-1090 Vienna, Austria
E Schober *consultant paediatrician*
Institute of Diabetes, Nutrition and Metabolic Diseases, N Paulescu, 79811 Bucharest 2, Romania
C Ionescu-Tirgoviste *consultant paediatrician*
Children's University Hospital, D-72070 Tübigen, Germany
A Neu *consultant paediatrician*
Correspondence to: P M Rothwell peter.rothwell@clneuro.ox.ac.uk

BMJ 1999;319:887–8

Republic); G Dahlquist (Sweden); A Green (Denmark); P Jarosz-Chobot (Poland); G Joner (Norway); D Michalkova (Slovakia); C Patterson (Northern Ireland); P Pozzilli (Italy, Lazio); AG Schranz (Malta); P Smail (Scotland); M Songini (Italy, Sardinia); B Urbonaite (Lithuania); E Wadsworth (British Paediatric Survey, UK).

Funding: The European diabetes (EURODIAB) research network is supported by the European Commission medical research programme (contracts BMH1-CT92-0043 and BMH4-CT96-0577).

Competing interests: None declared.

1 Leslie DG, Elliot RB. Early environmental events as a cause of IDDM. *Diabetes* 1994;43:843-50.
2 Hyoty H, Hiltunen M, Knip M, Laakkonen M, Vahasalo P, Karjalainen J, et al. A prospective study of the role of coxsackie B and other enterovirus infections in the pathogenesis of IDDM. *Diabetes* 1995;44:652-7.
3 Rothwell PM, Staines A, Smail P, Wadsworth E, McKinney P. Abnormal seasonality of birth in childhood diabetes. *BMJ* 1996;312:1456-7.
4 Jongbloet PH, Groenewould HMM, Hirasing RA, Van Buuren S. Seasonality of birth in patients with childhood diabetes in the Netherlands. *Diabetes Care* 1998;21:190-1.
5 Walter SD, Elwood JM. A test for the seasonality of events with a variable population at risk. *Br J Prev Soc Med* 1979;29:18-21.

(Accepted 4 May 1999)

Testicular neoplasia in cryptorchid boys at primary surgery: case series

Dina Cortes, Jakob Visfeldt, Henrik Møller, Jørgen Thorup

Department of Paediatric Surgery, 4072, Rigshospitalet, DK-2100 Copenhagen Ø, Denmark
Dina Cortes *registrar*
Jørgen Thorup *consultant paediatric surgeon*

Department of Pathology, Rigshospitalet
Jakob Visfeldt *professor*

Centre for Research in Health and Social Statistics, Danish National Research Foundation, DK-2100 Copenhagen Ø, Denmark
Henrik Møller *head*

Correspondence to:
J Thorup
J-Thorup@rh.dk

BMJ 1999;319:888–9

Cryptorchidism is associated with testicular cancer; the lifetime risk of 2-3% is about four times higher than in the general population.[1 2] Some groups of cryptorchid patients may have an especially high risk of testicular cancer.[3] Testicular carcinoma in situ is a well described histological pattern that precedes germ cell tumours.[1 4] We investigated whether it is possible at primary surgery to identify cryptorchid boys who have testicular neoplasia and therefore are at high risk of testicular cancer.

Method and results

We examined 1535 consecutive specimens of testicular tissue that were obtained from undescended testes at surgery for cryptorchidism in 1249 boys between 1971 and 1998. Previous reports have described 1026 of the biopsies in detail.[2 4] No patient had fallopian tubes or a uterus.

The table shows the total occurrence of testicular neoplasia at surgery for cryptorchidism. There was one case of invasive germ cell tumour, six cases of testicular carcinoma in situ, and one Sertoli cell tumour. Of the eight testes with neoplasia from seven patients, three neoplasms were diagnosed in intra-abdominal testes (cases 1-3), four occurred in three boys with abnormal external genitalia other than cryptorchidism (cases 4-6), and two were diagnosed in boys with known abnormal karyotype (cases 3 and 7).

All the case reports were reviewed. In the 97 boys (124 specimens) with intra-abdominal testes, three had known abnormal karyotype; 46,XY/47,XYY (case 3), 46,XYdel(11p), and 46,XY,13/20 unbalanced translocation; five had abnormal external genitalia, two with hypospadias, one with epispadias, and two with small penis and scrotum. Furthermore, 28 patients (38 specimens) had abnormal external genitalia but no intra-abdominal testes: 14 with hypospadias, two with epispadias, two with some ambiguity of the external genitalia (cases 4 and 5), two with hypoplastic scrotum, and eight with small penis and scrotum, of whom four had Kallmann's syndrome and one had testicular neoplasia (case 6). Moreover, 10 patients (14 specimens) had known abnormal karyotype: seven with 47,XXY;

Testicular neoplasia in eight undescended testes from seven cryptorchid boys, among 1249 patients who at median age 12.0 years (range 0.1-18.9 years) underwent surgery for cryptorchidism with examination of 1535 specimens of testicular tissue from undescended testes

Case No	Age at surgery for cryptorchidism	Anatomical position of testes	Record of testicular neoplasia and finding in contralateral testis	Characteristics
1	13.3 (right)	Intra-abdominal	Germ cell hypoplasia	Intra-abdominal testes, 46,XY; genitalia not abnormal
	13.3 (left)	Intra-abdominal	Carcinoma in situ testis	
2	5.4 (right)	Scrotum	Parents wanted no biopsy	Intra-abdominal testis, 46,XY; genitalia not abnormal
	5.4 (left)	Intra-abdominal	Carcinoma in situ testis	
3	7.1 (right)	Intra-abdominal	Large cell calcifying Sertoli cell tumor of testis	Intra-abdominal testes and abnormal karyotype; 46,XY/47,XYY; external genitalia not abnormal
	7.1 (left)	Intra-abdominal	No germ cells pattern	
4	10.2 (right)	External inguinal ring	Carcinoma in situ testis	Abnormal external genitalia; small penis, vaginal pouch, bifid scrotum, 46,XY[1]
	10.6 (left)	External inguinal ring	Carcinoma in situ testis	
5	10.9 (right)	External inguinal ring	Carcinoma in situ testis	Abnormal external genitalia; small penis and partially bifid hypoplastic scrotum[4]
	10.8 (left)	External inguinal ring	Germ cell hypoplasia	
6	18.6 (right)	Inguinal canal	Seminoma	Abnormal external genitalia; small penis and hypoplastic scrotum, 46,XY[4]
	18.6 (left)	External inguinal ring	Germ cell hypoplasia	
7	15.4 (right)	Inguinal canal	Carcinoma in situ testis	Abnormal karyotype; 45,X/46,XY[4]
	15.4 (left)	Scrotum*	Germ cell hypoplasia	

In total, the risk of testicular neoplasia at surgery for cryptorchidism in childhood was: 7/1249=0.56% (exact 95% confidence interval 0.28% to 1.15%; calculated by solving the exact binomial equations iteratively) per cryptorchid boy, and 8/1535=0.52% (0.27% to1.02%) per testicular specimen from an undescended testis.
*This biopsy from a scrotal testis was not included in the material of 1535 specimens of testicular tissue from undescended testes.