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Letters

Technical failure in photographic screening for diabetic retinopathy

Diabetic retinopathy is the largest single cause of registered blindness among people of working age. At any time, 10% of the diabetic population may have retinopathy requiring ophthalmological follow-up or treatment [1]. The two main approaches to diabetic retinopathy screening include regular ophthalmoscopic examination and retinal photography with subsequent grading. Digital fundus photography has greatly replaced slide and polaroid photography and is a cost-effective system. However, good quality images are essential for accurate grading to be possible. The National Screening Committee (NSC) recommends that the technical failure rate for digital fundus photography should be less than 5% (www.diabetic-retinopathy.screening.nhs.uk). In order to determine if this target is achievable, we have audited the technical failure rate at St James University Hospital.

We completed the audit cycle and looked at 150 consecutive retinal images in May 2002, and another 150 images in September 2002. The images were taken by two photographers, both of whom had received an initial training of 3 weeks to familiarize them with ophthalmic photography, and had 1 year of practical experience before the start of the study. Based on the National Screening Committee criteria, the set of images from each patient were classified as being a technical success or a technical failure due to photographic error, or a technical failure due to patient factors such as media opacity, small pupil or patients with difficulty in positioning. The images were considered a technical failure due to photographic error if the correct number of images had not been taken, the images were not centred well, or had poor clarity obscuring view of 1/3 or more of the temporal image or the large temporal blood vessels. If the image quality was poor, the photographers were asked to provide a red reflex image to demonstrate media opacity, small pupil, etc. With such supporting evidence, the images were to be considered technical failure due to media opacity. In its absence, it was presumed that it was a technical failure due to photographic error.

Our technical failure rate in this completed audit cycle was 7%. We could not achieve the recommended technical failure rate less than 5% as suggested by NSC. In all, there were 13 (4.3%) technical failures due to media opacity, small pupil or difficult positioning of the patient. This figure did not differ much between the audits, being six in the first audit and seven in the second. There were eight technical failures due to photographic error, five in the first audit and three in the second. It is possible that continued discussion with the photographers may reduce this figure further.

This study suggests that the technical failure rate is greatly dependent on patient variable factors like cataract, small pupil, etc. and hence may be difficult to achieve. However, if we are able to reduce the technical failure rate due to photographic error to less than 1%, and assuming that the images failing due to patient factor remain constant at around 4%, the standard proposed by NSC would be achievable.

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MAM conceived the idea for the paper and is the guarantor. AA was responsible for the data collection and the initial preparation of the manuscript. Both the authors discussed the core ideas, reviewed and edited the manuscript. Funding, none; competing interest, none.

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HLA, day care attendance, and socio-economic status in young patients with Type 1 diabetes

The aetiology of Type 1 diabetes is multifactorial. The HLA alleles *DQB1*0302* and *DQB1*0201* confer susceptibility with compound heterozygotes at highest risk [1,2]. However, the absolute risks from these alleles in the general population are fairly low: the 'high-risk' compound heterozygote genotype (~6%), other high-risk *DQB1*0302* and *DQB1*0201* genotypes (~1.3%) and very low-risk genotypes (= 0.3%) [1,3]. Although other genes may confer half of the genetic susceptibility [4], family and twin studies demonstrate variability in susceptibility that is not inherited [2], possibly owing to chance events in the developing T-cell receptor repertoire or to environmental factors [5,6]. Ecological studies of socio-economic status [7] and case–control studies of social mixing in infancy [8] show that proxies for increased exposure to infections are associated with protection against Type 1 diabetes, especially in younger children. However, such studies assessed only the marginal effect of the environment, genotype was not measured.

To test for a gene (*HLA-DQB1*)–environment (decreased exposure to infectious contacts, or higher socio-economic status) interaction in young children with Type 1 diabetes, we

Table 1

a. Demographic, socio-economic, environmental, and genotype distribution data

Demographic	
Gender	Males 40 (58%); females 29 (42%)
Decade of birth	1970s 2; 1980s 34; 1990s 33
Age at diagnosis	Mean 3.4 years; SD 1.5 years
Family history of Type 1 diabetes	Sibling, parent, or grandparent: 13/69 (19%)
Socio-economic	
Maternal education	High school graduation or greater: 62/69 (90%)
Paternal education	High school graduation or greater: 59/69 (86%)
Total family income	> £13 500: 58/69 (84%)
Household crowding	People per room: mean 0.39; SD 0.13
≤ 0.6 people per room	64/69 (93%)
Daytime companions less than 6 years	Mean 1.3; SD 1.6
Less than 2	50/69 (72%)
Genotype	
*DRB1*03*, *DQA1*0501*, *DQB1*0201/DRB1*04*, *DQA1*03011* (or **0303*, *n* = 3), *DQB1*0302*	25 (36%)
*DRB1*07*, *DQA1*0201*, *DQB1*0201/DRB1*04*, *DQA1*03011*, *DQB1*0302*	1 (0.1%)
*DRB1*03*, *DQA1*0501*, *DQB1*0201/DRB1*03*, *DQA1*0501*, *DQB1*0201*	7 (10%)
*DRB1*04*, *DQA1*03011*, *DQB1*0302/DRB1*04*, *DQA1*03011*, *DQB1*0302*	8 (12%)
*DRB1*03*, *DQA1*0501*, *DQB1*0201*/other	14 (20%)
*DRB1*04*, *DQA1*03011* (or **0303*, *n* = 2), *DQB1*0302*/other	7 (10%)
other/other	7 (10%)

b. Interactions between genotype and less than two daytime companions

Crude analysis: synergy index (SI) 0.77 (95% CI 0.26, 2.3)

Multivariate analyses		SI	(95% CI)		SI	(95% CI)	Breslow–Day *P*-value
Gender	Male	0.94	(0.24, 3.7)	Female	0.53	(0.09, 3.3)	0.62
Decade of birth	1970/1980s	1.40	(0.35, 5.7)	1990s	0.40	(0.07, 2.3)	0.27
Diagnosis before age 3.4 years	Yes	0.47	(0.11, 2.0)	No	1.62	(0.27, 9.9)	0.29
High socio–economic status	Yes	0.47	(0.12, 1.9)	No	1.67	(0.29, 9.7)	0.26

c. Interactions between genotype and high socio-economic status

Crude analysis: synergy index (SI) 0.39 (95% CI 0.14, 1.1)

Multivariate analyses		SI	(95% CI)		SI	(95% CI)	Breslow–Day *P*-value
Gender	Male	0.13	(0.03, 0.6)	Female	1.40	(0.30, 6.5)	0.03
Decade of birth	1970/1980s	0.25	(0.06, 1.0)	1990s	0.82	(0.16, 4.3)	0.28
Diagnosis before age 3.4 years	Yes	0.80	(0.19, 3.4)	No	0.18	(0.04, 0.8)	0.16
< 2 daytime companions	Yes	0.95	(0.14, 6.3)	No	0.27	(0.08, 0.9)	0.26

performed HLA typing of children diagnosed before age 6 years and administered a questionnaire on the child's social environment in the first year of life to their mothers. Participants were identified from the prevalent cases recorded in a population-based computerized diabetes database in a province with an ethnically diverse population and a stable high incidence (20.4/100 000 per year) of Type 1 diabetes [9]. Synergy indices (case only odds ratios) [10] and their 95% confidence intervals were calculated using SAS 6.12 software (SAS Institute Inc., Cary, NC, USA) as were *P*-values for the Breslow–Day test for homogeneity of the odds ratios for multivariate associations. This study design has been shown to be valid for gene–environment interaction if the exposure and genetic factor occur independently and the disease is rare [11]. It is also more efficient and perhaps superior to a case–control study as there are smaller standard errors due to the absence of the control group variability and the difficult selection of an unbiased control group is avoided [12]. The University of Manitoba Faculty of Medicine Research Ethics Board approved this study and informed consent was obtained for each participant.

Complete data were obtained from 69 of 144 eligible patients; the major reasons for non-participation were remote residence, disinterest, and refusal of venepuncture. Demographic, environmental, socio-economic and genotype data are shown in Table 1. In order to reduce misclassification, we defined socio-economic status as high only if the annual family income

was > £13 500, both parents were high school graduates, and household population density was < 0.6 people per room. Asking a single question about day care attendance was found to be unreliable as most respondents whose children were found on detailed questioning to be cared for outside the home during the day answered the single question in the negative.

Since 62/69 (90%) of patients had at least one high-risk allele, all main comparisons were restricted to testing for differences between the highest risk (*DQB1*0201/DQB1*0302*) compound heterozygote genotype and the others. A lower proportion of patients born in the most recent decade had the highest risk genotype (27% in the 1990s vs. 47% earlier). No statistically significant interaction was found between the number of daytime companions and the highest risk genotype [synergy index (SI) 0.77, 95% confidence interval (CI) 0.26, 2.3]; stratified analyses did not change this conclusion (Table 1). Furthermore, no statistically significant interaction was found between high socio-economic status and the highest risk genotype (SI 0.39, 95% CI 0.14, –1.1), although there was a statistically significant difference between the two gender strata, i.e. a lower risk in males with the combination of the highest risk genotype and high socio-economic status than would be expected jointly for genotype and environment.

As this is the first study on this topic, additional studies are required to confirm these results. A large well-maintained prospective cohort study including measurement of genotype and these early environmental exposures would avoid many limitations of the present study [13,14]. First, owing to the case-only design, we can test only whether a synergistic interaction exists, and if so, identify its direction. Without a control group, we cannot directly test the hygiene hypothesis. Second, larger numbers would allow results with narrower confidence intervals. Third, any concern that non-participation could bias the tests of interaction would be avoided by careful retention of participants. Our results are in agreement with previous studies showing that 90% of young children with Type 1 diabetes have at least one of the two highest risk *DQB1* alleles. The lower proportion of patients born in the most recent decade with the highest risk genotype may indicate the presence of some environmental factor that interacts with genotype to confer susceptibility to diabetes at a lower level of genetic risk [15].

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Use of insulin glargine during embryogenesis in a pregnant woman with Type 1 diabetes

Devlin *et al.* [1] recently reported the first use of the insulin analogue, glargine in a pregnant woman with Type 1 diabetes.

Treatment was initiated after finalized embryogenesis in the 14th week of pregnancy as the patient was suffering from recurrent nocturnal hypoglycaemic episodes. Good metabolic control was achieved and an uncomplicated progression of the pregnancy resulted. Here we present the case of a pregnant patient with Type 1 diabetes, who received insulin glargine during the entire embryogenesis period.

This 35-year-old mechanical constructor had developed Type 1 diabetes 3.5 years previously during her first pregnancy. That pregnancy ran without complications and her diabetes was well controlled throughout. In June 2000, the patient commenced treatment with 15 IU insulin glargine at bedtime as a basal insulin supply in the context of an intensified insulin regimen. Accounting for meal referral and dose adaptation, the patient also took approximately 25 IU of regular insulin per day. The total duration of treatment with insulin glargine was 25 months.

In April 2002, the patient became pregnant (unplanned) for a second time and after referring to the patient information leaflet, which does not specifically contraindicate the use of insulin glargine during pregnancy, she continued to take insulin glargine. At the 15th week of pregnancy she contacted her diabetologist; HbA_{1c} levels were 6.8% (reference < 6.1%) and ophthalmological and microalbuminuric screenings were negative. After being informed of the lack of information regarding the use of insulin glargine during pregnancy, the patient decided to discontinue this treatment. Following initiation of a basal supply of NPH insulin (6 IU) in the morning and a zinc sustained pig insulin (12–16 IU Semilente®) at bedtime, HbA_{1c} levels dropped to between 6.4% and 6.1% for the remainder of the pregnancy. Regular fetal ultrasonic investigations were normal.

In the 37th week, the patient gave birth to a healthy boy [weight 3810 g, body length 51 cm, American Pediatric Gross Assessment Record (APGAR) index 9-10-10] via vaginal delivery; forceps were used due to a birth stop. The neonate showed signs of transient hypoglycaemia [blood glucose 2.3–3.6 mmol/l (41–66 mg/day)] and received a 150-ml infusion of a 10% glucose solution in the first 24 h. No further complications occurred during the postpartal period. Furthermore, echocardiographic and ultrasonic investigations of the encephalon, abdomen and hips on days 1–3 after birth were normal.

No systematic investigations into the use of insulin glargine during pregnancy in humans have been reported to date, and thus it is not licensed for use in this context. Bioassays in rats and rabbits treated with insulin glargine demonstrated no direct effects on reproduction and embryo-fetal development. However, maternal and embryo-fetal toxicity was observed in rabbits treated with medium and high doses of insulin glargine, as well as with NPH insulin, and the effects were related to the hypoglycaemic action of insulin [2]. In conclusion, well-planned investigations are needed for a final benefit–risk assessment to be made of the use of insulin glargine during pregnancy.

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