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RESEARCH POINTERS

Perinatal characteristics and risk of rheumatoid arthritis

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The aetiology of rheumatoid arthritis is unknown. Perinatal factors may be implicated in the pathogenesis of the disease

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Rheumatoid arthritis is a disease of unknown aetiology. Twin studies indicate the importance of genetic as well as environmental factors.¹ In terms of environmental factors, few risk factors are well established, and, in practice, rheumatoid arthritis cannot be attributed to any specific exposure.² Descriptive studies imply a birth cohort effect in the incidence of rheumatoid arthritis.^{3 4} We assessed perinatal characteristics in relation to the risk of adult rheumatoid arthritis and observed associations with several perinatal exposures, including high birth weight and low frequency of breast feeding.

Participants, methods, and results

We selected participants from a local register of all patients seen either in the outpatient clinic at the

department of rheumatology at Malmö University Hospital, southern Sweden, or by any of the three private rheumatologists in the same city. The register contains over 90% of all known cases of rheumatoid arthritis in the catchment area. We selected 77 subjects in this register (all patients who were born between 1940 and 1960 and were still living in Malmö) as cases (median age of onset of rheumatoid arthritis 46 years, 76% (59) positive for rheumatoid factor, 85% (65) with erosive disease). For each case we selected the consecutive four births of the same sex at the same delivery unit in Malmö as controls (n=308). Using the population and census registers, we identified 98 controls who were still living in Malmö at the time of the investigation for a restricted analysis including only controls (and the corresponding cases) who were still living in the

Perinatal characteristics of cases of adult onset rheumatoid arthritis and matched controls in Malmö, Sweden

Characteristics	Cases (n=77)	Controls (n=308)	Odds ratio (95% CI)	
			Univariate*	Multivariate†
Categorical variables (No (%))				
Socioeconomic status of father:				
Manual worker	54 (81)	177 (64)	2.8 (1.3 to 5.7)	2.3 (1.1 to 4.9)
Non-manual worker	13 (19)	100 (36)	1.0	1.0
Birth weight (g):				
≥4000	16 (22)	32 (10)	3.3 (1.4 to 7.4)	3.6 (1.4 to 9.1)
3000-3999	42 (58)	224 (73)	1.0	1.0
<3000	15 (21)	52 (17)	1.4 (0.7 to 3.0)	1.8 (0.8 to 4.2)
Large for gestational age‡:				
Yes	9 (12)	8 (3)	4.4 (1.6 to 12)	
No	66 (88)	299 (97)	1.0	
Small for gestational age‡:				
Yes	5 (6)	23 (7)	1.0 (0.3 to 2.6)	
No	70 (91)	284 (93)	1.0	
Breast feeding started during postnatal hospital stay:				
Yes	68 (89)	293 (96)	0.2 (0.1 to 0.7)	0.1 (0.0 to 0.4)
No	8 (11)	11 (4)	1.0	1.0
Maternal diseases during pregnancy§:				
Yes	8 (10)	40 (13)	0.7 (0.3 to 1.8)	
No	69 (90)	268 (87)	1.0	
Older siblings at time of birth:				
Yes	44 (57)	155 (50)	1.4 (0.8 to 2.4)	
No	33 (43)	153 (50)	1.0	
Previous miscarriages in mother:				
Yes	9 (12)	36 (12)	1.0 (0.4 to 2.4)	
No	68 (88)	272 (88)	1.0	
Continuous variables (mean (SD))			Analysis of variance, matched version	
Placental weight (g)	628 (130)	610 (114)	P=0.21	
Maternal age at delivery (years)	28.4 (5.3)	28.3 (5.8)	P=0.85	
Gestational length (days)	281 (14)	281 (15)	P=0.74	
Hospital stay after delivery (days)	7.0 (3.0)	6.7 (2.7)	P=0.51	

When present, subjects with missing variables were not included in the analyses
*Relative risk expressed as univariate odds ratios conditional on the case-control matching with 95% confidence intervals.
†Multivariate conditional logistic regression with birth weight category, socioeconomic status of father, and breast feeding started during the postnatal hospital stay as independent variables in the model. Results are based on the 67 cases with non missing data on covariates and their matched controls.
‡Large (small) for gestational age was defined as those birth weights more (less) than 2 standard deviations above (below) the mean birth weight for gestational age according to the currently used Swedish reference curve.
§Any recorded intercurrent diseases in the records.

catchment area at the time of the investigation. One investigator (MEJ) undertook a structured review of the birth records of all cases and controls and extracted information on birth weight (categorised as <3000 g, 3000-4000 g, and >4000 g), length at birth, gestational length, weight of placenta, maternal diseases during pregnancy, maternal age, history of miscarriage, parity at time of birth of the case or control, length of hospital stay after delivery, start of breast feeding during the hospital stay after delivery, and paternal occupation (manual or non-manual worker). We calculated univariate and multivariate odds ratios by using conditional logistic regression to account for the matched design.

High birth weight (≥ 4000 g *v* 3000-3999 g) was positively associated with rheumatoid arthritis (odds ratio 3.3, 95% confidence interval 1.4 to 7.4; table), but low birth weight (<3000 g *v* 3000-4000 g) was not. Initiation of breast feeding during inpatient care after delivery (0.2, 0.1 to 0.7), and paternal occupation (manual *v* non-manual worker; 2.8, 1.3 to 5.7) were also associated with rheumatoid arthritis. The associations between birth weight, initiation of breast feeding, and paternal occupation were not confounded by each other (table). We found no other significant associations. Analyses using the restricted sample of only controls living in the catchment area at the time of the investigation resulted in similar risk estimates.

Comment

Our findings indicate that characteristics of the perinatal period may be of aetiological importance in the pathogenesis of rheumatoid arthritis. To our knowledge, this is the first study to assess markers of intrauterine and perinatal health in relation to adult rheumatoid arthritis, although preliminary data show that weight at 1 year of age is associated with seropositivity for rheumatoid factor in adult life.⁵

Our findings may be explained by several factors, including the development of the immune system in utero, perinatal or postnatal modulation of the immune system, and unmeasured confounding factors. The strengths of this report include the population based design, the independent identification of controls, and the fact that information on exposure was recorded before the occurrence of the outcome.

Contributors: LTHJ participated in conception and design, analyses, and interpretation of the data, drafting, and final approval of the article. MEJ participated in conception and design, analyses and interpretation of the data, drafting, and final approval of the article. JA participated in conception and design, interpretation of the data, critical review, and final approval of the article. WCK participated in conception and design, interpretation of the data, critical review, and final approval of the article. LTHJ is the guarantor.

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Competing interests: None declared.

Ethical approval: The study was approved by the ethics committee of Lund University.

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The way things were?

I had the opportunity to review a set of patient's notes recently while preparing her discharge summary, and I came across the following correspondence, for an unrelated condition, to her general medical practitioner in 1968.

"This poor lass seems to have got herself into a rather impossible situation. I think she is right in her assessment that she just cannot cope with both the home and this very trying job, forever having the public chasing her up on the telephone because the men have not delivered the coal. I imagine she is pretty conscientious and takes it all to heart a bit more than a person with less auburn hair in the family. She has in fact a sensitive skin and a sensitive soul; that seems to be the basis of her jitteriness and so on i.e. not thyrotoxicosis. The very slight thickening in the left upper thyroid is not outwith normal limits. I cannot see she will be happy unless she changes to a less frustrating job."

On reading this, I could not help but wonder if medical staff nowadays would even be allowed to send

this sort of correspondence, especially in today's increasingly litigious society. Perhaps this is but one measure of the way things were in the 1960s, or a reflection on how defensive we have since become. One from the archives to ponder.

Richard Mark Graham *senior house officer, Aberdeen Royal Infirmary*

We welcome articles up to 600 words on topics such as *A memorable patient*, *A paper that changed my practice*, *My most unfortunate mistake*, or any other piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk. Permission is needed from the patient or a relative if an identifiable patient is referred to. We also welcome contributions for "Endpieces," consisting of quotations of up to 80 words (but most are considerably shorter) from any source, ancient or modern, which have appealed to the reader.