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Maternal and perinatal risk factors for childhood cancer: record linkage study

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ABSTRACT

Objective: To investigate maternal and perinatal risk factors for childhood cancer.

Study design: Case–control analysis of linked records from the Aberdeen Maternity and Neonatal Databank with the Scottish Cancer Registry and the General Registry of Births and Deaths in Scotland was carried out.

Setting: Aberdeen, Scotland.

Participants: Cases (n=176) comprised children diagnosed with cancer under 15 years or recorded as having died of cancer. Four controls per case were matched by age and gender.

Risk factors tested: Maternal age, body mass index, social class, marital status and smoking as well as pre-eclampsia, antepartum haemorrhage and previous miscarriage, gestational age, birth weight and Apgar scores were compared between groups to test for association with cancer. ORs with 95% CIs were calculated using conditional logistic regression in univariable and multivariable models.

Results: Of the maternal characteristics tested, mother's age at delivery (cases mean 28.9 (SD 5.6) years vs controls mean 30.2 (SD 4.6), p=0.002) and smoking status (38.6% smokers among cases, 29.7% among controls, p=0.034) were found to be different between groups. Of the perinatal factors tested, low Apgar score at 5 min (adjusted OR (AOR) 4.59, 95% CI 1.52 to 13.87) and delivery by caesarean section (AOR 1.95, 95% CI 1.30 to 2.92) showed statistically significant associations with childhood cancer in the multivariable model.

Conclusions: Younger maternal age, maternal smoking, delivery by caesarean section and low Apgar score at 5 min were independently associated with increased risk of childhood cancer. These general findings should be interpreted with caution as this study did not have the power to detect any association with individual diagnostic categories of childhood cancer.

Strengths and limitations of this study

- Detailed and contemporaneous recording of data in the databases eliminated recall and reporting bias.
- The large number of social and demographic variables recorded in the Aberdeen Maternity and Neonatal Databank (AMND) enabled incorporation of most potential covariates in the analysis.
- Inadequate power to detect some weak associations reported previously in the literature.
- The number of cases according to site-specific cancer diagnosis was too small in our sample to allow any subgroup analysis.

INTRODUCTION

Childhood cancer has been increasing in Scotland. A published report estimates that its incidence has risen from an age standardised rate of 120 cases per million population in the time period 1983–1987 to 161 cases per million in the period 2003–2007.[1] The reason for this increasing trend remains unexplained as the aetiopathogenesis of childhood cancer is poorly understood. As most of the children present with cancer in the first few years of life, epidemiologists hypothesise that prenatal and perinatal exposures may have a part to play in its pathogenesis. The evidence surrounding this is, however, conflicting. While some researchers have found associations of younger maternal age at delivery[2] maternal anaemia,[3 4] history of miscarriage,[2 5 6] maternal overweight[7] and smoking[8] with some childhood cancers, others have found no such associations.[9–11] Fetal growth is perhaps the most investigated perinatal risk factor for childhood cancer[7 12 13]; but the authors report conflicting results. While specific central nervous system tumours have been found to be associated with intrauterine growth restriction (IUGR), the overall risk was small.[12] Therefore, apart from the associations with Down's syndrome and in utero exposure to radiation, research into the maternal and perinatal risk factors has remained inconsistent, the results limited by small sample sizes and recall or reporting bias.

Our objective was, therefore, to investigate the maternal and perinatal risk factors for childhood cancer, specifically to examine the effects of IUGR, preterm birth and birth asphyxia on the development of childhood

cancer in the offspring, taking advantage of the opportunities offered by record linkage of a cancer registry with a local birth register.

METHODS

Data sources

The Aberdeen Maternity and Neonatal Databank (AMND) holds data for all Aberdeen City births from 1950 to the present, and includes all reproductive events to women resident in a defined geographical area with a relatively stable population. The AMND records all births occurring at the Aberdeen Maternity Hospital, the only maternity hospital serving the population of Aberdeen city and district. The exposure variables in terms of potential maternal and perinatal risk factors were derived from the AMND. The Scottish Cancer Registry has been in existence since 1951 and was complete up to 2010, at the time of the present analysis. The cases of childhood cancer were identified from this register.

Data linkage

All children born between 1993 and 2006 were identified from the AMND. Their records were linked to the Cancer Registry in Scotland (SMR 06) and the General Registry of Births and Deaths in Scotland (GRO-S), using deterministic matching. The linkage was carried out by data analysts from the Information and Services Division of National Health Service (NHS) Scotland using Community Health Index (CHI) numbers. The CHI number is a number unique to all individuals registered with a general practice in Scotland and recorded in both databases used in this study. In a small proportion of cases where CHI number was not available (6%), probabilistic matching using surname, date of birth and postcode was used. After data linkage, all identifying information, including CHI numbers, were removed, and an anonymised dataset was provided for analysis.

Study design

A case–control study design was employed. Cases comprised all children identified as above from the AMND who were diagnosed with cancer under 15 years of age in Scotland as recorded in the Scottish Cancer Registry or recorded as having died of cancer. Controls were selected from the pool of children not diagnosed as having cancer, matched by age and gender using four controls per case.

Twins and multiple births were excluded as were stillbirths and early neonatal deaths. As Down's syndrome is known to be associated with a higher risk of acute lymphoblastic leukaemia (ALL) as well as myeloid leukaemia of Down's syndrome, all cases of diagnosed Down's syndrome were excluded. Moreover, those children who had died of non-cancer causes prior to their 15th birthday, as identified from GRO-S, were also excluded.

Exposure and outcome variables used in the analysis

Maternal sociodemographic factors such as age at delivery, body mass index, Registrar General's occupation-based social class, marital status, history of miscarriage and smoking habits were extracted from the AMND. Any complications recorded during the index pregnancy such as pre-eclampsia, gestational hypertension and antepartum haemorrhage as well as mode of delivery, gestational age at delivery, birth weight, Standardised Birthweight Score[14] and Apgar score at 1 and 5 min were also extracted. Data extractors were blind to the case–control status of the individual children.

The outcome variables obtained from the Cancer Registry in Scotland were in the form of a binary variable (yes/no) indicating whether or not a cancer record was present, and, if present, the site of cancer was given as per International Classification of Diseases (ICD) codes. Similarly, death records with up to 10 different causes of death given by ICD codes were obtained from linking with GRO-S.

Statistical analysis

All analyses were conducted using STATA V.11 (STATA Corp, Texas, USA). Maternal baseline characteristics were compared between children diagnosed with cancer and controls using independent two-sample t tests and χ^2 tests. Maternal complications such as gestational hypertension, pre-eclampsia, antepartum haemorrhage and history of miscarriage were compared between the cases and controls using univariate conditional regression to calculate ORs with 95% CIs. Similarly, perinatal factors such as gestation at birth, birth weight, IUGR measured by Standardised Birthweight Score and Apgar score at 1 and 5 min were also tested in univariate models for any association with childhood cancer. Then a multivariable conditional logistic regression model was fitted that included as independent variables all the risk factors tested on univariate analysis. The possibility of cancer subgroup analysis was considered according to the International Classification of Childhood Cancer (ICCC), but the number of cases in each subgroup was too small to warrant this.

Missing data

Apart from the variables describing maternal baseline characteristics, the other risk factors did not have any missing values. There were 18 controls and 1 case with missing smoking data. The multivariable model was repeated including and excluding the individuals with missing information. We used two methodological approaches to handle this—listwise deletion—that is, not including any group where one person in that group has missing data, and imputation by creation of a missing value (999) so that all cases and controls were included in the analyses. The ORs obtained by both methods are presented.

RESULTS

There were 62 375 deliveries between 1993 and 2006 as identified from the AMND. After excluding Down's syndrome cases, twins and multiple births, stillbirths and early neonatal deaths, there were 60 117 children eligible for linkage with the Cancer Registry. It was possible to link 43 591 of these children to the cancer and GRO-S databases. Among the children with linked data, 106 had died of non-cancer causes before they reached the age of 15 and were therefore excluded from the analysis. Of the remainder, 176 children were found to have a record in the Cancer Registry, giving a cumulative incidence rate of childhood cancer up to 15 years of 4.05 per 1000 deliveries. They constituted the cases for the analysis and were matched in a 1 : 4 ratio by year of birth and sex from the pool of remaining children without any records of cancer to obtain 704 controls. As D40, D44, D47 and D48 codes in ICD-10 do not correspond to cancer diagnosis in ICCC, the analyses were repeated excluding these codes.

Maternal baseline characteristics were compared between cases and matched controls in table 1. Of the maternal characteristics tested, mother's age at delivery (cases mean 28.9 years, SD 5.6; controls mean 30.2, SD 4.6; p=0.002) and smoking status (38.6% current or ex-smokers among cases, 29.7% among controls, p=0.022) were found to be significantly different between the two groups.

Table 2 presents the unadjusted ORs with 95% CIs for all the perinatal potential risk factors for childhood cancer. Of the factors tested, preterm birth (OR 2.23 (1.31 to 3.79)), low birth weight (OR 1.87 (1.03 to 3.39)), low Apgar score at 5 min (OR 5.01 (1.73 to 14.54)) and delivery by caesarean section (OR 1.77 (1.23 to 2.56)) were found to be statistically significant. Subsequently, these factors were adjusted for maternal age at delivery and smoking. As the maternal smoking variable had some missing data, we handled this using two approaches—listwise deletion and imputation of a missing value. After these adjustments, low birth weight no longer remained significant, but the other associations were strengthened.

After conducting the univariate analyses, multivariable models were fitted including maternal age, smoking status, pre-eclampsia, placenta praevia, preterm birth, low birth weight, low Apgar at 5 min and delivery by caesarean as independent variables (results in table 3). Similar to the previous analyses, we used two methods of listwise deletion and imputation of the missing value to adjust for smoking status. Of the perinatal factors tested, Apgar score below 7 at 5 min (adjusted OR (AOR) 3.91, 95% CI 1.13 to 13.61 (listwise deletion); AOR 4.59, 95% CI 1.52 to 13.87 (imputation)) and delivery by caesarean section (AOR 2.11, 95% CI 1.38 to 3.23 (listwise deletion); AOR 1.95, 95% CI 1.30 to 2.92 (imputation)) showed statistically significant associations with childhood cancer in both multivariable models adjusted for maternal age, smoking and other factors simultaneously included in the models. Preterm birth (delivery before 37 completed weeks of gestation) and low birth weight, defined as a birth weight below 2500 g, showed a significant association in the univariate analysis, but these associations were no longer significant in the multivariable model. The associations were not statistically significant on univariate or multivariable analysis between the risk of childhood cancer and hypertensive disorders,

Table 1 Comparison of maternal baseline characteristics between case children and control children

Characteristics	Cases	Controls	p Value
Age at delivery (mean, SD)	28.9 (5.6)	30.2 (4.6)	0.002
Maternal social class			
Manual	26 (14.8%)	79 (11.2%)	0.187
Non-manual	62 (35.2%)	295 (41.9%)	
Single/widowed	87 (49.4%)	325 (46.2%)	
Missing	1 (0.6%)	5 (0.7%)	
Paternal social class			
Paternal manual	71 (40.3%)	329 (46.7%)	0.193
Paternal non-manual	47 (26.7%)	183 (26.0%)	
Maternal non-manual	57 (32.4%)	184 (26.1%)	
Missing	1 (0.6%)	8 (1.1%)	
Marital status			
Single/widowed/divorced/separated	62 (35.2%)	222 (31.5%)	0.324
Married	113 (64.2%)	482 (68.4%)	
Missing	1 (0.6%)	0 (0%)	
BMI (mean, SD; missing cases=12, missing controls=39)	25.2 (5.1)	25.5 (5.1)	0.407
Smoking			
Non-smoker	107 (60.8%)	477 (67.8%)	0.034
Smoker/ex-smoker	68 (38.6%)	209 (29.7%)	
Missing	1 (0.6%)	18 (2.6%)	

BMI, body mass index.

Table 2 Comparison of perinatal factors between cases and controls with statistically significant ORs shown in italics

Perinatal factors	Cases N=176, %	Controls N=704, %	Unadjusted OR (95% CI)	Age and smoking adjusted OR (95% CI) —listwise deletion	Age and smoking adjusted OR (95% CI) —imputation of missing value
Pre-eclampsia	11 (6.3)	23 (3.3)	1.98 (0.94 to 4.18)	1.94 (0.88 to 4.28)	1.92 (0.91 to 4.09)
Gestational hypertension	19 (10.8)	71 (10.1)	1.09 (0.62 to 1.89)	1.21 (0.67 to 2.17)	1.13 (0.64 to 2.01)
Placenta praevia	3 (1.7)	4 (0.6)	3.00 (0.67 to 13.40)	3.46 (0.76 to 15.65)	3.45 (0.76 to 15.62)
Abruption	1 (0.6)	4 (0.6)	1.00 (0.11 to 8.95)	1.31 (0.14 to 12.66)	1.04 (0.12 to 9.41)
Other APH	19 (10.8)	77 (10.9)	0.99 (0.58 to 1.68)	0.98 (0.56 to 1.72)	0.96 (0.56 to 1.65)
Previous miscarriage	18 (10.2)	103 (14.6)	0.67 (0.39 to 1.13)	0.83 (0.48 to 1.43)	0.70 (0.41 to 1.19)
Preterm birth	24 (13.6)	47 (6.7)	*2.23 (1.31 to 3.79)*	*2.09 (1.16 to 3.76)*	*2.23 (1.29 to 3.85)*
Low birth weight	17 (9.7)	38 (5.4)	*1.87 (1.03 to 3.39)*	1.81 (0.94 to 3.45)	1.78 (0.97 to 3.28)
Low Apgar at 1 min	30 (17.1)	107 (15.4)	1.14 (0.73 to 1.78)	1.14 (0.71 to 1.84)	1.15 (0.73 to 1.81)
Low Apgar at 5 min	8 (4.6)	7 (1.0)	*5.01 (1.73 to 14.54)*	*4.91 (1.46 to 16.51)*	*5.70 (1.93 to 16.78)*
Delivery by caesarean	55 (31.3)	143 (20.4)	*1.77 (1.23 to 2.56)*	*2.25 (1.50 to 3.36)*	*2.07 (1.41 to 3.05)*
Instrumental delivery	26 (14.8)	144 (20.5)	0.66 (0.41 to 1.04)	0.68 (0.41 to 1.13)	0.67 (0.42 to 1.08)
Intrauterine growth restriction	23 (13.4)	71 (10.3)	1.41 (0.85 to 2.36)	1.20 (0.68 to 2.12)	1.35 (0.80 to 2.23)

APH, antepartum haemorrhage.

antepartum haemorrhage, history of miscarriage or IUGR. Unlike the Apgar score at 5 min, the score at 1 min did not show any association with childhood cancer.

We further investigated the types of preterm delivery (spontaneous or induced) and caesarean section (elective or emergency) as risk factors for childhood cancer and found that spontaneous and induced preterm delivery were significantly associated in the adjusted model but only delivery by emergency caesarean section remained significant on subgroup analysis (AOR 1.43, 95% CI 1.20 to 2.18). Furthermore, we found that the commonest indication for caesarean delivery in the infants who were subsequently diagnosed with cancer was fetal distress (data not shown).

Table 3 ORs from multivariable model

Perinatal factors	OR (95% CI) from multivariable model—listwise deletion*	OR (95% CI) from multivariable model—imputation of missing value*
Pre-eclampsia	1.56 (0.68 to 3.59)	1.55 (0.70 to 3.44)
Placenta praevia	1.64 (0.32 to 8.34)	1.65 (0.32 to 8.43)
Preterm birth	1.60 (0.76 to 3.37)	1.85 (0.92 to 3.72)
Low birth weight	1.00 (0.44 to 2.28)	0.90 (0.41 to 1.97)
Low Apgar at 5 min	*3.91 (1.13 to 13.61)*	*4.59 (1.52 to 13.87)*
Delivery by caesarean	*2.11 (1.38 to 3.23)*	*1.95 (1.30 to 2.92)*

Statistically significant ORs are shown in italics.
*All variables adjusted for maternal age and smoking and for other variables in the model.

Table 4 shows the distribution of cancer sites in the 176 cases. As this table shows, the commonest sites were the brain and haemopoietic organs, especially leukaemia, but the number of cases in the subgroups was too small to allow any meaningful analysis.

DISCUSSION

We aimed to study the maternal and perinatal risk factors at the time of birth associated with the diagnosis of childhood cancer using record linkage between two-high quality registers in Scotland. We found a positive association between younger maternal age at delivery and maternal smoking with childhood cancer. In addition, preterm birth before 37 weeks of gestation, Apgar score below 7 at 5 min and delivery by emergency caesarean section showed statistically significant associations with childhood cancer, the last two of which remained significant in the adjusted models.

Childhood cancer is a rare condition. Case–control studies are therefore the most efficient epidemiological study design to study several risk factors at the time of birth. Cancer registries across the world have been utilised to identify cases, but finding appropriate controls remains problematic. Moreover, data collections regarding exposures by means of interviews or questionnaires are subject to recall and reporting bias. More recently, linkage of birth registers with cancer registries has been utilised to design large-scale cohort studies. However, the routine data collection is liable to lack sufficiently detailed data regarding exposure and potential confounding factors. We have tried to minimise these problems by linking two high-quality registers in Scotland. Previous validation projects have shown these databases to be 100% complete and over 97% accurate.[15] Detailed

Table 4 Distribution of sites of cancer

Cancer site	Number	Per cent
C22—liver and intrahepatic bile ducts	2	1.14
C34—bronchus and lung	2	1.14
C41—bone and articular cartilage of other and unspecified sites	10	5.68
C49—other connective and soft tissue	7	3.98
C52—vagina	5	2.84
C56—ovary	3	1.70
C62—testis	12	6.82
C64—kidney except renal pelvis	7	3.98
C69—eye and adnexa	6	3.41
C71—brain	27	15.34
C72—spinal cord, cranial nerves, other CNS	3	1.70
C74—adrenal gland	6	3.41
C75—other endocrine glands and related structures	4	2.27
C76—other and ill-defined sites	2	1.14
C83—diffuse non-Hodgkin's lymphoma	3	1.70
C85—other and unspecified non-Hodgkin's	2	1.14
C91—lymphoid leukaemia	37	21.02
C92—myeloid leukaemia	10	5.68
C94—other leukaemias of specified cell type	2	1.14
D32—meninges	3	1.70
D40—Uncertain/unknown behaviour male genital	2	1.14
D43—uncertain/unknown behaviour brain and CNS	2	1.14
D44—uncertain/unknown behaviour Endocrine	1	0.57
D47—uncertain/unknown behaviour of lymphoid, haematopoietic and related tissue	9	5.11
D48—uncertain/unknown behaviour unknown sites	9	5.11

CNS, central nervous system.

and contemporaneous recording of obstetric data in the AMND eliminated recall and reporting bias. The large number of social and demographic variables recorded in the AMND enabled incorporation of most potential covariates in the analysis. Despite these strengths to our study design, we were limited by the small number of cases and it is possible that we did not have sufficient power to detect some weak associations reported previously in the literature. Maternal and perinatal risk factors for childhood cancer appear to differ by the site of cancer in the published literature. The number of cases according to site-specific cancer diagnosis was too small in our sample to allow any subgroup analysis. Furthermore, morphology codes were not available for us to carry out more appropriate groupings of childhood cancers. This, coupled with the fact that we had to conduct our analyses on *all* cancers, would have made it less likely for us to find the associations that exist with site-specific cancers. This could be a major limitation of the current analysis. There was a single case of cancer that occurred within the first year of delivery. It is possible that this could be the result of the cancer being already present at birth.

The association of parental age with the diagnosis of cancer in general as well as in specific sites has been studied before. Johnson *et al*,[16] in a pooled analysis of register linkage data from several US states, found that the risk of childhood cancer increased with increasing maternal age, while paternal age appeared to have no effect on the risk. On the other hand, several other studies, similar to the current analysis, have shown that younger maternal age was associated with an increased childhood cancer risk.[2 17] There could be several explanations for the disparate findings. In a register linkage study carried out in Sweden,[18 19] researchers found that the advancing maternal age was positively associated with childhood cancer risk but only in a historical cohort. This association disappeared in a recent cohort of women although the reasons for this are unknown. Moreover, Schutz[20] suggests that the association of lower maternal age at the time of delivery with leukaemia in the offspring could be explained by non-response bias, although this is not applicable to the present study.

The relationship between maternal smoking and childhood cancer in the offspring is complex and controversial. While Sorahan *et al*[21–23] and Edraki and Rambod[24] found an increased overall risk of childhood cancer with paternal cigarette smoking, there did not appear to be an association with maternal smoking after adjusting for birth weight. Furthermore, Pang *et al*[9] did not find evidence of smoking as a risk factor for childhood cancer after adjusting for parental age. Similar associations were reported by Chang *et al*[25] with regard to ALL. The evidence appears to indicate that neonatal passive smoking plays a more important role than in utero transfer of maternal smoke-related toxins, although we cannot rule out the possibility of an association between maternal smoking and site-specific cancers.[26 27] For the current analysis, we did not have access to data on paternal smoking habits and the association seen with maternal smoking could be due to this variable acting as proxy for paternal smoking.

Other associations noted in this study have been reported before—preterm birth[28] and low Apgar score.[2 28] Li *et al*[29] found a 46% increased risk of childhood cancer in infants who had a low 5 min Apgar score. Birth weight has received a lot of attention as a risk factor for childhood cancer. While brain tumours and retinoblastoma appear to be associated with high birth weight[30–32] others have found hepatoblastomas[7 33] and gliomas[34] to be associated with very low birth weight infants. Schmidt *et al*[28] observed a U-shaped relationship between birth weight and cancer risk, while Podvin *et al*[35] found birth weight adjusted for gestational age to be a better predictor than birth weight alone for the

diagnosis of ALL, lending support to our findings. It is, however, important to note that we did not find an association with IUGR as measured by the z-score or standardised birth weight score. Dorak *et al*[36] noted an association between birth weight and a diagnosis of ALL which was gender dependent, showing a non-linear association in boys.

Few studies have assessed the mode of delivery, specifically caesarean delivery, as a possible risk factor for the development of childhood cancer. Those studies have found a weak-to-moderate association[3 7 10 37 38] between caesarean delivery and subsequent risk of developing ALL. Several hypotheses can be developed regarding the biological mechanism underpinning this association. First, caesarean delivery is likely to be a marker of adverse pregnancy and delivery events—indeed, our finding of increased emergency caesarean rates, indicated by fetal distress, seems to support this hypothesis. However, the association remained and actually became stronger, after adjusting for most other possible pregnancy complications. It was customary to use 100% oxygen to resuscitate infants born by caesarean section in the past. It is possible that this could have played a role in the subsequent development of cancer. The last explanation involves epigenetic modulations at birth. Schlinzig *et al*[39] have demonstrated altered DNA methylation in cord white blood cells after caesarean delivery and suggested that this may be the basis of increased risk of asthma, diabetes and ALL seen in infants born by caesarean section.

The association of caesarean delivery with childhood cancer seen in this analysis should be treated with caution given the small number of childhood cancer cases in the study. The recent National Institute of Health and Care Excellence (NICE) guidelines[40] recommend caesarean delivery on maternal request. However, we have to remember that the majority of the caesarean deliveries seen in the cases of childhood cancer in the current analysis were emergency procedures with strong indications such as fetal distress. Our finding of the strong association of childhood cancer with caesarean delivery warrants further research using record linkage of larger cohorts or prospective follow-up of birth cohorts. From the point of view of public health interventions, the only other modifiable risk factor appears to be parental smoking. Several population-based lifestyle interventions are already under way to reduce the prevalence of smoking in pregnancy.

CONCLUSION

We found a positive association between younger maternal age at delivery and maternal smoking with childhood cancer. In addition, preterm birth, low Apgar score at 5 min and delivery by caesarean section showed associations with childhood cancer, which remained significant even after controlling for various covariates. These general findings should be interpreted with caution as this study did not have the power to detect any association with individual diagnostic categories of childhood cancer.

Contributors SB was responsible for designing the study, facilitating data extraction, supervising data analysis and writing of the first draft of the paper; MB analysed the data; SB, GJM and DP conceived the research idea and GJM was responsible for overall supervision. All authors contributed to the writing of the final draft of the paper. SB is the guarantor.

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Competing interests None.

Ethics approval This research proposal was approved by the Privacy Advisory Committee of the Information and Services Division National Health Service (NHS) Scotland and the steering group of the Aberdeen Maternity and Neonatal Databank. Formal ethical approval was not considered necessary by North of Scotland Research Ethics Service as only anonymised data were analysed in this study.

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