Risk factors associated with juvenile idiopathic arthritis: A study from Eastern India

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Abstract

Introduction: There are limited studies which suggest that environmental risk factors or early life exposures, like low birth weight, lack of breast feeding, passive smoking, recurrent childhood infections may have a role in the aetio-pathogenesis of paediatric autoimmune diseases like juvenile idiopathic arthritis (JIA).

Objectives: To study the association of environmental and early risk factors with the development of JIA in a tertiary care hospital in Eastern India.

Method: This case control study was conducted in the Paediatric Rheumatology Clinic of Vivekananda Institute of Medical Sciences (VIMS), India, over a period of 1 year. Enrolled JIA cases, who consented to be a part of the study, were asked to identify at least 2 to 3 healthy playmates of similar age and sex as controls. A 2-page structured oral questionnaire pertaining to environmental and early life risk factors was prepared and patients/controls or their caregivers were asked to answer these.

Results*:* Birth weight, gestational age, mode of delivery, breast feeding, passive smoking and infections in infancy were not significantly associated with the development of JIA. There was a significant association with sun exposure ($p < 0.05$), non-vegetarian diet ($p<0.05$) and use of mosquito repellent ($p<0.05$)

Conclusions: Among the various risk factors assessed we found that in our study there was a significant association of sun exposure ($p < 0.05$), non-vegetarian diet ($p<0.05$) and use of mosquito repellents ($p < 0.05$) with the development of JIA.

(Key words: Environment, JIA, Case-control study)

Introduction

Juvenile Idiopathic Arthritis (JIA) is the commonest cause of chronic arthritis in children less than 16 years of age[1]. It is believed that genetically susceptible individuals, when subjected to changes in environment for a considerable period of time, may be at risk for developing JIA. A Swedish population-based case control study concluded that infections in early life may be a contributory factor for the development of JIA in later life[2]. An Australian case control study did not find any association with breast feeding but noted an inverse relationship with paternal smoking[3]. A study from USA found premature birth to be associated with an increased risk of JIA[4]. In a study from Utah spanning more than a decade, no significant association was found between small particulate matter concentration and risk of JIA[5]. So far, though there has been some research on environmental triggers in adults from India[6], no such studies have been reported in the paediatric age group.

Objectives

To study the association of environmental and early risk factors with the development of JIA in a tertiary care hospital in Eastern India.

Method

The study was conducted at the Paediatric Rheumatology Clinic at Vivekananda Institute of Medical Sciences (VIMS), a major tertiary care hospital in Eastern India over a period of one year, from 2020-2021.

Sample size: Consecutive JIA patients (meeting the criteria of International League Against Rheumatism) attending the paediatric rheumatology outpatient department (OPD) were selected as cases. The cases were asked to identify at least 2-3 healthy playmates of a similar age. Age-matched healthy playmates of the cases from a similar environmental background were taken as controls. Unfortunately, during the pandemic era some JIA patients could not come for follow-up due to lockdown, economic and other issues. Of the 50

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JIA patients who turned up, 41 consented to participate. Healthy controls were selected from their playmates. To increase the power of the test, we chose a 1:2 case control ratio.

Parents and caregivers of cases and controls were given a 2-page questionnaire pertaining to exposure to early life risk factors over a period of two years prior to the development of the JIA symptoms.

The questionnaire consisted of vital statistical details including age, sex and, Body Mass Index (BMI) at the time of survey. Based on previous published data, the questionnaire consisted of the following environmental factors: gestational age, birthweight, mode of delivery, breastfeeding and duration, age of introduction of cow milk, passive smoking, dietary history (vegetarian/non-vegetarian), stressful life events (death in family, separation of parents, loss of job of parents etc.), domestic pets, exposure to household pollutants like insecticides, cooking fuel used (Liquid petroleum gas /wood), environmental pollution (mainly automobile) source of drinking water, duration of sunlight exposure in the first six months of life, type of house (concrete/mud)

Ethical issues: Approval for the study was obtained from the Institutional Ethics Committee of Ramakrishna Mission Seva Pratishthan, Vivekananda Institute of Medical Sciences, West Bengal, India on 9th February 2022. Written informed consent was obtained from the parents of the participant children.

Statistical analysis: The characteristics of the participants were summarised separately for cases and the playmate matched controls. The continuous variables were represented as mean ± standard deviation. The representation of categorical variables was done using counts and percentages. Cases and the playmate - matched controls were analysed by logistic regression (reported as odds ratios (OR) and associated 95% confidence intervals (CI)) separately for each risk factor of interest along with the p-value for each factor. $p< 0.05$ was considered significant. Statistical analysis were conducted using SPSS software.

Results

Fifty JIA cases attending the Paediatric Rheumatology OPD were approached to enrol in the study. Of these 9 declined and hence we had 41 cases who consented to participate in the study. The mean age of the cases was 11.2 ± 4.13 years. For each of the 41 cases at least 2 healthy playmates responded to the questionnaire. So eventually we had 41 cases and 82 controls. Mean age of the controls was 11.17 ±3.23 years. Of the 41 JIA cases, 15 were enthesitis-related arthritis, 10 were systemic onset variety, 8 were polyarticular, 5 were oligoarticular and 3 were psoriatic.

Table 1 shows the demographic characteristics of the cases and playmate-matched controls.

Cases were predominantly female (65.9%). They were born at term, >2.5kg at birth, born of vaginal delivery and introduced to cow milk after 1year of age. Compared to controls they were more exposed to passive smoking, house-hold pets and mosquito repellents.

Table 2 gives the risk factors for environment/early life exposures in JIA cases and age-matched controls.

Perinatal factors: Birth weight, gestational age and mode of delivery were not significantly associated with the development of JIA. However low birth weight (<2.5kg), preterm delivery (<37weeks) lowered the odds of developing JIA with respect to the reference levels.

Environmental factors: The environmental factors found to have a significant association with JIA were sunlight exposure, use of mosquito repellents and intake of non-vegetarian food. Sun exposure was seen to have a significant association with JIA. The odds of JIA increased with exposure time in the sun. ($p < 0.05$ for sun exposure of 30min-1 hour and exposure >1 hour) when compared to no exposure to sun. Diet had a significant effect on JIA. The odds of JIA decreased with intake of non-vegetarian diet as compared to vegetarian diet ($p <0.05$, OR 0.170, 95%CI: 0.034- 0.843). Use of mosquito repellent could be seen as a significant factor. No use of mosquito repellent decreased the odds of JIA as compared to those who used mosquito repellents. ($p <0.05$, OR 0.183, 95%CI: 0.038-0.867). However, from this study we also came across some environmental factors which lowered the risk of developing JIA though significant association could not be demonstrated. The OR of using tap water was 0.428 (reference water from tube well) implying tap water lowered odds of developing JIA. Non exposure to passive smoking, household pets, environmental air pollution, pesticides lowered the odds of developing jia with respect to their reference levels.

When compared to the reference group of breastfeeding of <6 months, those who breast fed for 6-12 months showed reduced chance of developing JIA. The odds of developing JIA were more if the child was not exposed to infections in the first year of life.

Table1: ***Demographic features of juvenile idiopathic arthritis cases and playmate-matched controls***

Factor	**Category**	**Controls** ***(n=82)*** ***n (%)***	**Cases** ***(n=41)*** ***n (%)***
Gender	Female	38 (46.3)	27 (65.9)
	Male	44 (53.7)	14 (34.1)
Caste	Hindu	67 (81.7)	32 (78.0)
	Muslim	15 (18.3)	09 (22.0)
Annual income	<1.5L	51 (62.2)	24 (58.5)
	>1.5L	31 (37.8)	17 (41.5)
Birth weight	<2.5kg	21 (25.6)	09 (22.0)
	>2.5kg	61 (74.4)	32 (78.0)
Mode of delivery	Caesarean section	29 (35.4)	10 (24,4)
	Vaginal delivery	53 (64.6)	31 (75.6)
Gestational age (weeks)	<37	18 (22.0)	05 (12.2)
	>37	64 (78.0)	36 (87.8)
Passive smoking	No	61 (74.4)	20 (48.8)
	Yes	21 (25.6)	21 (51.2)
Duration of breast feeding	<6 months	13 (15.9)	11 (26.8)
	6-12 months	30 (36.6)	13 (31.7)
	>12 months	39 (47.6)	17 (41.5)
Infection in first year of life	No	77 (93.9)	37 (90.2)
	Yes	05 (06.1)	04 (09.8)
Cow milk introduction	<1 year	24 (29.3)	16 (39.0)
	>1 year	53 (64.6)	22 (53.7)
	No	05 (06.1)	03 (07.3)
House hold pets	No	68 (82.9)	14 (34.1)
	Yes	14 (17.1)	27 (65.9)
Mental stress	No	75 (91.5)	31 (75.6)
	Yes	07 (08.5)	10 (24.4)
House type	kacha	15 (18.3)	12 (29.3)
	pukka	67 (81.7)	29 (70.7)
Duration of sun exposure	<30 min	16 (19.5)	02 (04.9)
	30 min – 1 hour	03 (03.7)	12 (29.3)
	>1 hour	09 (11.0)	15 (36.6)
	No	54 (65.9)	12 (29.3)
Diet	Non-vegetarian	26 (31.7)	20 (48.8)
	Vegetarian	56 (68.3)	21 (51.2)
Drink water source	Tube-well	38 (46.3)	21 (51.2)
	Tap	44 (53.7)	20 (48.8)
Exposure to pesticide	No	71 (86.6)	22 (53.7)
	Yes	11 (13.4)	19 (46,3)
Exposure to environmental pollution	No	67 (81.7)	26 (63.4)
	Yes	15 (18.3)	15 (36.6)
Use of mosquito repellent	No	58 (70.7)	21 (51.2)
	Yes	24 (29.3)	20 (48.8)
Cooking fuel	LPG	60 (73.2)	17 (41.5)
	Wood	20 (24.4)	11 (26.8)
	Both	01 (01.2)	10 (24.4)
	Others (kerosene)	01 (01.2)	03 (07.3)
Consanguinity	No	72 (87.8)	37 (87.8)
	Yes	10 (12.2)	04 (09.8)

Table 2: ***Risk factors for environmental/early life exposures in JIA cases and age-matched controls***

Factor	p-value	Exp (B)	95% CI for Exp (B)	
			Lower	Upper
Gender				
Male	Reference			
Female	0.812	1.188	0.286	4.933
Annual income				
>1.5 Lac	Reference			
<1.5 Lac	0.071	0.198	0.034	1.148
Birth weight				
>2.5 kg	Reference			
<2.5 kg	0.599	0.575	0.073	4.538
Mode of delivery				
NVD	Reference			
LSCS	0.972	0.973	0.202	4.680
Gestational period				
>37 weeks	Reference			
<37 weeks	0.289	0.286	0.028	2.892
Passive smoking				
Yes	Reference			
No	0.755	0.747	0.120	4.644
Duration of breast feeding				
< 6 months	Reference			
6-12 months	0.592	0.563	0.069	4.599
>12 months	0.768	1.346	0.186	9.730
Infection(<1year)				
Yes	Reference			
No	0.816	1.389	0.088	21.986
Cow milk introduction				
No	Reference			
<1 year	0.610	0.511	0.039	6.727
>1 year	0.468	0.374	0.026	5.317
Pets				
Yes	Reference			
No	0.137	0.255	0.042	1.545
Mental stress				
Yes	Reference			
No	0.313	0.371	0.054	2.542
House type				
pucca	Reference			
kacha	0.473	0.461	0.056	3.819
Sun exposure				
No	Reference			
<30 minutes	0.700	1.675	0.121	23.100
30min-1 hour	0.007	22.877	2.368	221.015
>1 hour	0.006	12.455	2.047	75.792
Diet				
Non vegetarian	Reference			
Vegetarian	0.030	0.170	0.034	0.843
Drinking water				
Tube well	Reference			
Tap	0.324	0.482	0.113	2.060
Exposure to pesticide				
Yes	Reference			
No	0.476	0.490	0.069	3.480
Exposure to environmental pollution				
Yes	Reference			
No	0.238	0.303	0.042	2.202
Cooking fuel				
Wood	Reference			
Both	0.053	21.294	0.965	469.779
LPG	0.381	0.374	0.042	3.367
Others	0.901	1.246	0.039	39.879
Mosquito repellent				
Yes	Reference			
No	0.032	0.183	0.038	0.867
Constant	0.035	428.780		

Discussion

This case-control study looked into the various early life and environmental risk factors associations for the development of JIA. The factors which were found to have significant associations in our study included dietary influences, sunlight exposure and insecticides, mainly mosquito repellent.

Previous studies[6] have shown that there is an inverse relation between sunlight exposure and development of JIA. This has been attributed to the fact that UV exposure leads to increased levels of circulating vitamin D in our body. The active metabolite 1,25(OH)D leads to downregulation of cytokine release mainly IL12, Th1 and Th 17 which are believed to play an important role in the pathogenesis of JIA. In our study, however, we found a direct relationship between JIA and sun exposure. Children who were born during winter and who had prolonged sun exposure in the early months of infancy had an increased risk of developing JIA ($p<0.05$). A similar observation was made by Berkun Y, *et al*[7] who studied the seasonality of birth pattern of children with JIA compared to the general population and concluded that those born between November to March had an increased incidence of JIA compared to those born in the summer months. This study supported the hypothesis that the autoimmune process may have begun *in utero* or the perinatal period due to seasonal environmental variation. Ultra-violet light from sunlight leads to oxidative stress and result in DNA damage and production of autoantigens and autoreactive T cells which may accelerate the autoimmune process.

Diet was found to have a significant association with JIA. Children on a non-vegetarian diet were significantly more prone to develop JIA ($p<0.05$) compared to those on a vegetarian diet. The non-vegetarian diet mainly comprised of eggs, poultry and red meat. Previous investigations have shown that a period of fasting followed by a vegetarian diet can actually decrease disease activity[8]. Pattison DJ, *et al*[9] conducted a retrospective study to analyse the dietary risk factors for the development of inflammatory arthritis, matching 88 new patients with inflammatory arthritis with 176 controls. They concluded that a high level of protein consumption, especially meat and meat products may be an independent risk factor for the development of inflammatory arthritis. A study of Seventh -Day Adventists in California[10] also suggested that meat consumption was related to arthritis, although most such cases were unlikely to have been rheumatoid arthritis. Though there is limited data, the occurrence of rheumatoid arthritis is also lower in Mediterranean countries, where consumption of meat is lower compared to Western countries. The exact aetiology of this association is not known. It has been postulated that the high iron content of meat, especially red meat, may cause some oxidative reaction in synovial membrane of joints leading to their inflammation. Further, it has been suggested that high collagen content of meat leads to collagen sensitisation and production of anti-collagen antibodies in susceptible individuals. However, another study from NHS[11] failed to demonstrate any association with animal protein intake and risk of rheumatoid arthritis in adults.

Although the use of farming and agricultural pesticides has been associated with autoimmune diseases, the risk with household and personal insecticide is not known. Among household pollutants, we found that the common offender was mosquito repellents. It was observed that those who have used mosquito repellents in their houses, had a significantly ($p<0.05$) higher risk of developing JIA compared to age-matched controls. Parks CG, *et al*[12] in his study involving post-menopausal women, observed that personal and workplace use of insecticides was associated with an increased risk of rheumatoid arthritis and SLE. We however could not find any such association in the paediatric population. Regarding other household pollutants, like cooking fuel, we did not find any association.

The study population had principally two sources of drinking water, tap and deep tube well. We observed that cases who had tap water as the drinking source showed lower risk (OR 0.428) of JIA. Deep tube well provides ground water which has a high content of minerals like arsenic, fluoride, nitrates, manganese, sulphites and lead. Apart from enteral diseases, chronic ingestion may lead to long-term problems like liver and cardiac injury and may also predispose to autoimmune diseases. In a study by Das N, *et al*[13] involving a district in rural Bengal, it was seen that exposure to heavily contaminated ground water increased serum levels of ANA, anti-dsDNA and IL-6 in the study group, leading to joint pain and muscle cramps.

Non exposure to environmental air pollution, pesticides and passive smoking also lowered the odds ratio for JIA risk. This has also been observed in previous studies. A case-control study by Butz AM, *et al*[14] also showed that the risk of JIA is higher in children exposed to passive smoking. However, another Australian study showed contradictory results[3]. The use of pesticides and risk of autoimmune disease, including JIA, have been extensively reported[15,16]. In a follow up study spanning more than a decade, Zeft AS, *et al*[5] examined the short-term exposure to small particulate matter in a case-crossover design in 250 patients in the USA and Canada and found no significant association between air pollution and risk of SOJIA.

Risk of JIA was lower in children who were breast fed for 6 to 12 months compared to children breast fed less than 6 months. However, effects of breast feeding and JIA risk have shown varied results. While a US based case-control study[17] demonstrated that breast feeding for more than 3 months was protective against JIA, a German study[14] suggested increased risk of JIA with breast feeding.

Birth weight, gestational age and mode of delivery were not significantly associated with the development of JIA. However low birth weight (<2.5kg), preterm delivery (<37weeks) lowered the odds of developing JIA with respect to the reference levels. Low birth weight was protective against JIA, as was found in a German case-control study[18]. However, a Washington based case-control study did not show any effect of birth weight on JIA risk[4] but found premature birth to be associated with increased risk of JIA.

Regarding infections, we observed that odds of developing JIA was more if not exposed to infections in infancy. Regarding infections and autoimmune diseases there have been conflicting observations. While a few controlled studies[7,19] have suggested that infections may trigger development of JIA, the hygiene hypothesis on the contrary, brings to light that increased exposure to infections in early life may actually be protective for the development of autoimmune diseases[21]. However, a small US based playmate-matched case-control study[19], did not find any association between infection and JIA.

The major limitation of our study was the small population and the fact that it was conducted over a short time. In the future more studies involving large numbers would be needed to draw a conclusive inference

Regarding exposure to risk factors, though there were some differences with other western studies, it brought to light that some environmental and early life exposures may prove to be risk factors for the development of JIA in our Indian cohort too.

Conclusions

From this case-control study we inferred that sunlight exposure in early infancy, use of mosquito repellents and consumption of non-vegetarian diet were significantly associated with the risk of development of JIA in our cohort of Indian children.

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References

1. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, *et al.* International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: 2nd revision, Edmonton, 2001. *Journal of Rheumatology* 2004; **31**(2): 390-2.

2. Carlens C, Jacobson L, Brandt L, Cnattingius S, Stephansson O, Askling J. Perinatal characteristics, early life infections and later risk of rheumatoid arthritis and juvenile idiopathic arthritis. *Annals of Rheumatic Diseases* 2009; **68**(7): 1159-64. https://doi.org/10.1136/ard.2008.089342 PMid: 18957482

3. Ellis JA, Ponsonby AL, Pezic A, Chavez RA, Allen RC, Akikusa JD, *et al.* CLARITY- Childhood arthritis risk factor identification study. *Pediatric Rheumatology* 2012; **10**: 37. https://doi.org/10.1186/1546-0096-10-37 PMid: 23153063 PMCid: PMC3551677

4. Shenoi S, Shaffer ML, Wallace CA. Environmental risk factors and early life exposures in juvenile idiopathic arthritis. *Arthritis Care and Research* 2016; **68**(8): 1186-94. https://doi.org/10.1002/acr.22806 PMid: 26618899 PMCid: PMC5515549

5. Zeft AS, Prahalad S, Lefevre S, Clifford B, Mcnally B. Bohnsack JF, Pope CA. Juvenile idiopathic arthritis and exposure to fine particulate air pollution. *Clinical and Experimental Rheumatology* 2009; **27**(5): 877-84.

6. Thorsen ST, Pipper CB. No association between vitamin D levels around time of birth and later developing oligo-and polyarticular juvenile idiopathic arthritis: a Danish case-control study. *Scandinavian Journal of Rheumatology* 2016; **46**(2): 1-8. https://doi.org/10.1080/03009742.2016.1178325 PMid: 27460412

7. Berkun Y, Padeh S. Environmental factors and the geoepidemiology of juvenile idiopathic arthritis. *Autoimmunity Reviews* 2010; **9**(5): A319-24.

https://doi.org/10.1016/j.autrev.2009.11.018
PMid: 19932890

8. Muller H, de Toledo FW, Resch KL. Fasting followed by vegetarian diet in patients with rheumatoid arthritis: a systemic review. *Scandinavian Journal of Rheumatology* 2009; **30**:1-10.

9. Pattison DJ, Symmons DPM, Lunt M, Welch A, Luben R, Bingham SA, *et al.* Dietary risk factors for the development of inflammatory polyarthritis: evidence for a role of high level of red meat consumption. *Arthritis and Rheumatism* 2004; **50**(12): 3804-12.
https://doi.org/10.1002/art.20731
PMid: 15593211

10. Fraser GE. Diet, life expectancy and chronic diseases: Study of Seventh Day Adventists and other vegetarians. New York: Oxford University Press; 2003.

11. Benito-Garcia E, Feskanich D, Hu FB, Mandl LA, Karlson EW. Protein, iron and meat consumption and risk factor for rheumatoid arthritis: a prospective cohort study. *Arthritis Research and Therapy* 2007; **9**: R16.
https://doi.org/10.1186/ar2123
PMid: 17288585 PMCid: PMC1860075

12. Parks CG, Walitt BT, Pettinger M, Chen JC, DeRoos AJ, Hunt J, *et al*. Insecticide use and risk of rheumatoid arthritis and SLE in the women's health initiative observational study. *Arthritis Care and Research* 2011; **63**(2): 184-94.
https://doi.org/10.1002/acr.20335
PMid: 20740609 PMCid: PMC3593584

13. Das N, Paul S, Chatterjee D, Banerjee N, Majumder NS, Sarma N, *et al.* Arsenic exposure through drinking water increases the risk of liver and cardiovascular diseases in the population of West Bengal, India. *BMC Public Health*.2012; **12**: 639.
https://doi.org/10.1186/1471-2458-12-639
PMid: 22883023 PMCid: PMC3441389

14. Butz AM, Rosenstein BJ. Passive smoking among children with chronic respiratory disease. *Journal of Asthma* 1992; **29**(4): 265-72.
https://doi.org/10.3109/02770909209048941
PMid: 1634451

15. Koureas M, Rachiotis G, Tsakalof A, Hadjichristodoulou C. Increased frequency of rheumatoid arthritis and allergic rhinitis among pesticides sprayers and associations with pesticide use. *International Journal of Environmental Research and Public Health* 2017; **14**(8): 865.
https://doi.org/10.3390/ijerph14080865
PMid: 28763046 PMCid: PMC5580569

16. Parks CG, D'Aloisio AA, Sandler DP. Childhood residential and agricultural pesticide exposures in relation to adult-onset rheumatoid arthritis in women. *American Journal of Epidemiology* 2018; **187**(2): 214-23.
https://doi.org/10.1093/aje/kwx224
PMid: 29020148 PMCid: PMC5860218

17. Mason T, Rabinovich CE, Fredrickson DD, Amoroso K, Reed AM, Stein LD, *et al.* Breast feeding and the development of juvenile rheumatoid arthritis. *Journal of Rheumatology*1995; **22**(6):1166-70.

18. Radon K, Windstetter D, Poluda D, Haffner R, Thomas S, Michels H, *et al.* Exposure to animals and the risk of oligoarticular juvenile idiopathic arthritis: A multicenter case-control study. *BMC Musculoskeletal Disorders* 2010; **11**:73
https://doi.org/10.1186/1471-2474-11-73
PMid: 20403210 PMCid: PMC2873462

19. Rigante D, Bosco A, Esposito S. The aetiology of juvenile idiopathic arthritis. *Clinical Reviews in Allergy and Immunology* 2015; **49**(2): 253-61.
https://doi.org/10.1007/s12016-014-8460-9
PMid: 25384710

20. Ellis JA, Munro JE, Ponsoby AL. Possible environmental determinants of juvenile idiopathic arthritis. *Rheumatology (Oxford)* 2010; **49**(3): 411-25.
https://doi.org/10.1093/rheumatology/kep383
PMid: 19965974