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Socio-demographic and antenatal risk factors of brain tumor in children and young people: A matched case-control study from Karachi, Pakistan

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Abstract

Background: Brain tumors are a common cause of morbidity, disability, cognitive deterioration and mortality in children, even after treatment. Little is know about the specific causes. The study aimed to assess potential socio-demographic and antenatal factors in primary brain tumor (PBTs) in children and young people (CYP) in Karachi, Pakistan.

Designs and methods: A single center hospital based matched case control study in Karachi, Pakistan. Cases were defined as CYP aged between 5 and 21 years with any histological type and grade of primary brain tumor of any histology, stage or grade. Data were collected from parents of 244 patients at the selected center between 2017 and 2021 via telephonic interview. Controls were 5–21 years old CYP admitted with non-oncological diagnoses matched on age and sex. Matched Odds Ratios for predictors of brain tumor in children were derived. Those of statistical significance were included in a multivariable logistic regression model.

Results: In the adjusted model, lower paternal education (matched adjusted odds ratio (maOR) 2.46; 95% CI 1.09–5.55), higher household monthly income (maOR 3.4; 95% CI 1.1–10.2), antenatal paternal use of addictive substances (maOR 19.5; 95% CI 2.1–179.8), and antenatal maternal use of analgesics during pregnancy (maOR 3.0; 95% CI 1.2–7.9) were all independently predictive of brain tumors.

Conclusion: This matched case-control study found novel associations between maternal use of analgesics, paternal use of addictive substances, higher household income, and lower paternal education and Primary Brain Tumors in Children and Young People. Longitudinal multicenter studies will be required to test these associations prospectively.

Keywords

Brain tumor, antenatal factors, socio-demographic factors, children and young people, matched case control

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Introduction

Central nervous system (CNS) tumors account for approximately 20% of all childhood malignancies[1] and the second most common group of cancers in this age group. In Pakistan, data from the Karachi Cancer Registry shows the age-standardized incidence rate of CNS tumors among children of 3.14 per 100,000 while in adolescent 0.58 per 100,000.[2] Primary brain tumors (PBTs) in children and young people (CYP) age 0–24 years old[1] are a diverse group of neoplasms with unique histopathology, molecular features, and etiology. Tumor histology, location, age at diagnosis, sex, race, and ethnicity all correlate prognosis.[1]

Little is known regarding the pathogenesis of most PBTs in CYP. However, certain genetic syndromes, such as Neurofibromatosis type 1 and 2, Fanconi anemia and tuberous sclerosis have been associated with increased risk to develop brain tumors.[3] Moreover, family history of brain tumor has also found to be associated with PBTs in CYP.[4] Other reported or suspected nongenetic risk factors include, younger age of the child,[5] male gender,[6] higher parental age at the time of conception,[3] non-ionizing radiation, exposure to allergens, high birth weight of the child, exposure to infections early in life, greater parental age, high socioeconomic status, and exposure to pesticides.[1,4,7–9] N-nitroso compounds, parental smoking, and maternal antenatal use of hair dye are hypothesized to be associated with PBTs as well, though conclusive evidence is lacking.[10]

Most of the literature comes from high-income countries and data from lower-middle-income countries (LMICs) like Pakistan is scarce. The poor prognosis compels the continued search for potentially reversible factors that might be addressed to prevent disease. This study aimed to identify socio-demographic and antenatal factors by using a matched control study design.

Methodology

Study design and setting

A matched case-control study was conducted. A matched cases and controls based on specific characteristics allows for better control of potential confounding variables. By matching cases and controls on age and gender that are the potential confounders we tried to minimize the potential influence of these variables on the outcome leading to a more accurate assessment of the exposure-disease relationship. Individual matching was done that is, for each case a control was selected who closely resembled the case in terms of the matching criteria (age and gender). The patients were recruited from the Aga Khan University Hospital (AKUH), which is a Joint Commission International Accreditation (JCIA-accredited) private tertiary care hospital in Karachi. AKU is the largest children′s oncology referral center in Pakistan. Children are referred from the city, province and whole country.

Study participants

Cases were defined as children and young people (CYP) aged between 5 and 21 years[1] with PBTs of any histology, stage or grade presenting to a tertiary care hospital of Karachi, Pakistan between 2017 and 2021. Controls were 5 and 21 years old CYP admitted with non-oncological diagnoses matched on age and sex presenting to AKUH contemporaneously. Only CYP with parents who spoke and understood either Urdu or English were considered. CYP whose parents refused to consent were excluded.

Sampling strategy and data collection

Purposive sampling technique was employed to select participants. We identified cases diagnosed between 1st January 2017 and 31st December 2021 from Health Information Management Services (HIMS) in AKUH. Data were collected from the parents of the cases and controls via telephonic interview using a predesigned questionnaire developed by the investigators based on previously reported antenatal factors of brain tumor (Figure 1). The questionnaire comprised of child related factors such as; demographics (age, gender, province of residence, mother tongue), family history of brain tumor or other cancer, gestational age and birth order. The questionnaire also included information on parental factors such as; demographics (age, educational status, and household income) and antenatal factors such as; parental age at child's birth, parental use of addictives, parental smoking, maternal use of medications, maternal consumption of cured meat, maternal exposure to pesticides, ultrasound & X-ray, maternal use of hair spray or hair color and maternal comorbidities.[4]

Sample size

The sample size was calculated on PASS (Power Analysis and Sample Size) 11 software licensed by NCSS. In previous studies, the probability of exposure (higher parental age, parental education, socioeconomic status and antenatal factors) among sampled control patients ranged between 16% and 70%[4,7,10,11] with 26% of the controls having a high socioeconomic status.[8] A minimum sample of 122 CYP with PBTs (cases) was calculated. For each CYP with PBT, a matching sample of 1 control CYP, matched on age and sex was also obtained. This sample of 244 patients achieved an 80% power to detect an odds ratio of 2.5 versus the alternative of equal odds using a chi-square test with a 0.05 significance level.[4,7,10,11]

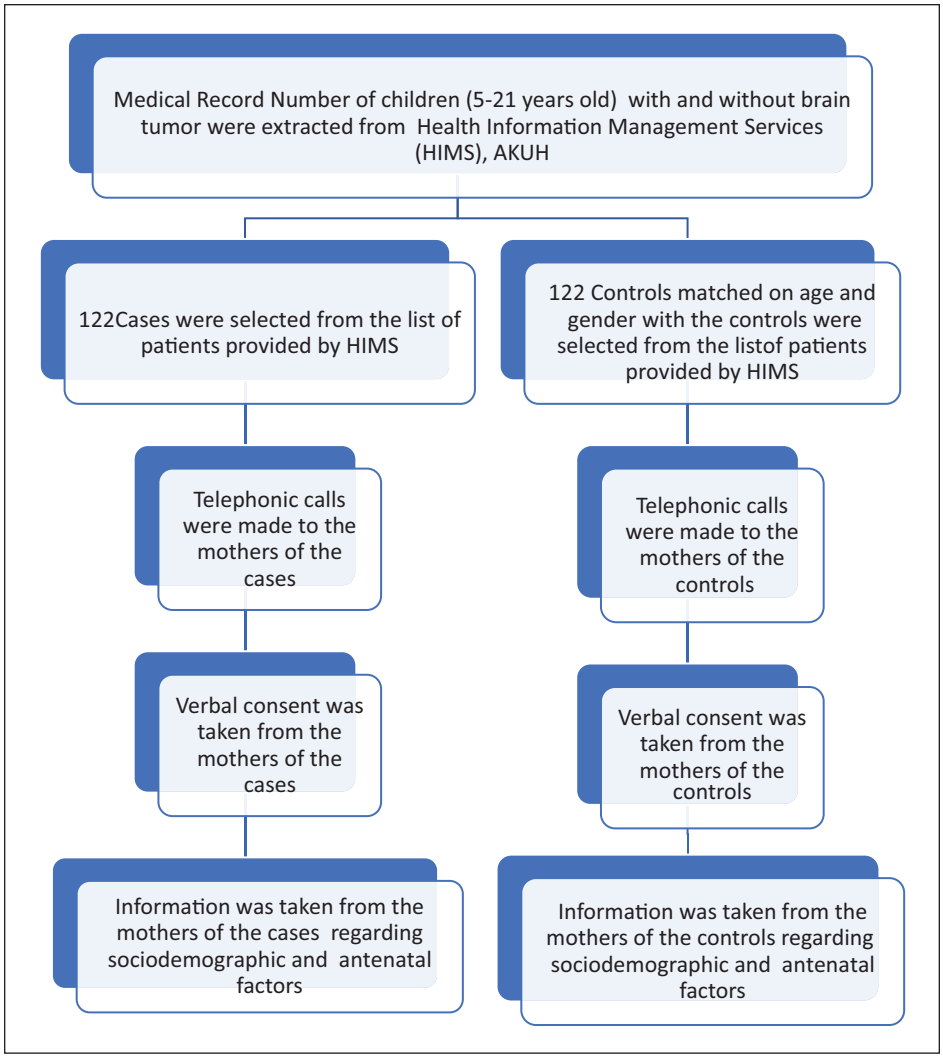

Figure 1. Flow of the study.

Ethical considerations

Ethical/institutional review committee AKU-ERC approval was obtained (ERC# 2020-4859-11855). Verbal consent was taken from the parents of the cases and controls after explaining the study procedure and its potential risks and benefits to them in Urdu or English as appropriate. All study materials containing personal identifiers were kept in a locked file cabinet. A unique study identification number was assigned to each participant. Data were entered in a password-protected electronic database that was only accessible to the research team.

Statistical analysis

Data were analyzed using STATA version 12. Results were presented as mean and standard deviation/ median (IQR) for normally and non-normally numeric variables. Comparison of numeric variables were made using independent sample *t*-tests/Mann-Whitney *U*-Test, as appropriate. Categorical variables were reported as frequency and percentages and compared using Chi-squared/Fisher exact tests as appropriate. Correlations to identify collinearity were performed using Pearson's correlation. Unadjusted and adjusted matched odds ratio (maOR) with their 95% CI were reported by using conditional logistic regression to determine the association of socio-economic and antenatal factors with brain tumor in CYP. A p-value < 0.2 was used as the screening cut-off on univariate analysis. A $p < 0.05$ for multivariable analysis was considered statistically significant throughout the study.

Results

A total of 122 cases and 122 controls were recruited. Description of cases and controls are shown in Table 1.

Socio-demographic factors

A higher proportion of cases versus controls were from the province of Punjab. Both maternal and paternal years of

Table 1. Diagnosis of children and young people with and without Brain tumor.

Cases (tumor location) *n* = 122	*n* (%)
Infratentorial tumor	48 (39)
Supratentorial tumor	46 (38)
Suprasellar tumor	22 (18)
Sellar tumor	6 (5)
Controls (diagnosis) *n* = 122	***n* (%)**
Fever	22 (18.0)
Orthopedic issues	19 (15.5)
Gastrointestinal issues	16 (13.1)
Appendicitis	12 (9.8)
Trauma	10 (8.2)
Birth defects	6 (4.9)
Endocrine problems	5 (4.1)
Neurological issues	5 (4.1)
Respiratory illness	4 (3.3)
Viral hepatitis	3 (2.5)
Other illness (Circumcision bleed, hearing loss, testicular torsion, urinary tract infection, inguinal hernia, hypertension, palpitation, deviated nasal septum, adenoids, and intake of rodenticide)	20 (16.4)

education were higher among parents of controls than cases. Fathers of controls were more likely to have received education of secondary and above as compared to the cases (Table 2).

Antenatal factors

The paternal mean age at child's birth was significantly lower in cases than controls. Paternal use of addictive substances was higher in cases (9%) than controls (0.8%). A higher proportion of mothers of cases used pain relievers and anti-emetics during pregnancy (16.4% vs 7.4% and 23% vs 11.5%) respectively as compared to the controls. These findings are shown in Table 3.

Logistic regression

Multivariable logistic regression was performed, matched for age and sex, while adjusting for covariates identified via univariate screening (Table 4). The factors that were associated with the outcome included: high family income, paternal use of addictive substances, maternal use of pain killers and lower paternal education. It was observed that the odds of a higher monthly income of >Rs 80,000 (>$397.6)/(>€373.57) was 3.4 times significantly higher in cases as compared to controls. Moreover, the odds of paternal use of addictive was 19.5 times significantly higher in cases as compared to controls. Maternal use of pain killers was also 3.7 times significantly higher in cases versus controls. However, the odds of fathers having no education or primary education was 2.46 times significantly higher in cases as compared to controls.

Discussion

Our results found maternal use of analgesics, paternal use of addictive substances, higher household income, and lower paternal education, to be statistically significant, independent factors of PBTs in CYP. Our study also found that analgesics use during pregnancy were reported by more than 60% women, whether by prescription or self-medication. This is a new finding: previous literature has shown associations with perinatal opioid use, but not other non-opioid analgesia and pain-killers in general are not associated with the development of pediatric cancers.[8,12–14]

Our study also found that paternal use of addictive substances to be associated with a 20-times increased risk of offspring developing PBTs. Though a 2014 meta-analysis found no relationship between paternal smoking before or during pregnancy,[12] the strength of the relationship in our study warrants a closer look. A meta-analysis in 2016 concluded that maternal smoking during pregnancy increases the risk of PBTs in offspring,[13] suggesting that the exposure to carcinogenic substances in cigarette smoke may be a risk factor. However, in our study, there were too few maternal smokers to explore this. LMICs, like Pakistan, have significantly higher rates of indoor. smokers, which increases second-hand exposure to cigarette smoke amongst household members.[14] In Pakistan, more than 40% of pregnant women are exposed to second-hand smoke in quantities sufficient to cause adverse health outcomes in the fetus and offspring.[15] Thus, it is possible that maternal exposure to second-hand smoke, due to paternal use of addictive substance such as smoking during pregnancy, may account for the statistically significant association with PBTs in CYP observed in our study.

We also identified higher household income to be statistically significant, independent risk factor for the development of PBTs in CYP. The trend of better economic status being associated with development of PBTs has been observed in different settings globally.[8,9] While the reasons for this association are yet poorly understood and likely to vary across different countries and settings, a few possible links have been identified. These include exposure to causal risk factors, behavioral differences, underlying racial differences, and even greater case ascertainment amongst higher economic groups due to better access to healthcare.[9] Given that Pakistan is a LMIC where access to cancer care is severely restricted amongst the lower socio-economic strata of the population,[16] the latter explanation likely contributes to our findings. This case ascertainment bias is further amplified in Pakistan, where the lack of insurance or government coverage means that the majority

Table 2. Socio-demographic characteristics of the study participants.

Socio-demographic factors	Cases ($n = 122$) n (%)	Controls ($n = 122$) n (%)	p Value
a. Child factors			
Mean age of child (years)	13.3 ± 4.36	13.6 ± 4.38	0.68
Gender			0.89
Male	76 (62)	76 (62)	
Female	46 (38)	46 (38)	
Province of residence			<0.001*
Sindh	72 (59)	99 (81)	
Punjab	26 (21)	05 (4)	
Baluchistan	09 (7)	10 (8)	
Khyber Pakhtun Khwa	10 (8)	03 (2)	
Gilgit Baltistan	05 (4)	05 (4)	
Mother tongue			0.04*
Sindhi	16 (13)	20 (16)	
Urdu	49 (40)	53 (43)	
Pushto	12 (10)	07 (5)	
Punjabi	18 (15)	15 (12)	
Balochi	05 (4)	08 (7)	
Saraiki	11 (9)	01 (1)	
Others[a]	11 (9)	18 (15)	
Mean gestational age (weeks)	37 ± 3.47	38 ± 1.28	0.14
Birth order			0.06
1	38 (31)	45 (37)	
2	35 (29)	45 (37)	
3+	49 (40)	32 (26)	
Family history of brain tumor-yes	13 (11)	5 (4)	0.05
Family history of any other cancer-yes	28 (23)	20 (16)	0.19
b. Parental factors			
Mother had any formal schooling-Yes	92 (75)	100 (82)	0.21
Median mother's years of education (years)	12 (12-14)	14 (12–14)	0.04**
Mother working-yes	14 (12)	12 (10)	0.67
Father had any formal schooling-yes	101 (83)	109 (89)	0.14
Median Paternal years of education	12 (10-16)	14 (12–16)	0.02**
Paternal education			0.02*
No education or primary	29 (24)	15 (12)	
Secondary and above	93 (76)	107 (88)	
Father working-yes	110 (90)	119 (98)	0.01**
Household monthly income (PKR/USD/Euro)[b]			0.22
<Rs 40,000 ($198.8)/(€186.79)	65 (53)	66 (54)	
Rs 40,000–80,000 ($198.8–397.6)/(€ 186.79–373.57)	40 (33)	47 (39)	
>Rs 80,000 (>$397.6)/(>€373.57)	17 (14)	9 (7)	

[a]Others for the variable mother tongue includes: Brushia (1), Burushaski (3), Chitrali (2), Haryanvi (1), Hazargi (1), Hindko (2), Kachi (1), Kashmiri (1), Kostan (1), Marvari (1), Memoni (7), Satri (1), and Shina (7).
[b]Exchange rate USD to PKR 202; Euro to PKR 215.
*Significant at p value <0.05 by using Chi square or Fisher exact test.
**Significant at p value <0.05 by using Mann Whitney U test.

of healthcare costs are borne out-of-pocket by patients.[17] Our study may additionally have been prone to a selection bias, since both cases and controls were recruited from one of the best equipped private hospitals in the country, where pediatric neuro-oncologic care can be afforded out-of-pocket only by patients from more privileged economic backgrounds. The distribution of provinces of residency across our study participants corroborates this point, as more than 40% of CYP with PBTs had traveled from different provinces across Pakistan to seek care at AKUH, indicating the financial means to seek healthcare at one of the country's top hospitals.

Lastly, our findings also demonstrated a higher risk of PBTs in CYP whose fathers were less educated. While

Table 3. Antenatal characteristics of study participants.

Antenatal factors	Cases ($N = 122$)	Control ($N = 122$)	p-value
Mean maternal age at child's birth	25.63 ± 5.26	26.72 ± 5.81	0.126
Range	13–48	29–44	
Mean paternal age at child's birth	30.45 ± 6.43	32.24 ± 6.88	0.037*
Range	43–58	41–59	
Maternal smoking during pregnancy	1 (0.8)	0 (0)	0.31
Paternal smoking during pregnancy	35 (28.7)	30 (24.6)	0.46
Maternal use of any addictive/tobacco	2 (1.6)	0 (0)	0.15
Paternal use of any addictive/tobacco	11 (9)	1 (0.8)	0.003*
Maternal use of vitamin B12, folate and iron	77 (63.1)	82 (67.2)	0.50
Maternal use of anti-hypertensive	2 (1.6)	0 (0)	0.15
Maternal use of diuretics	0 (0)	0 (0)	>0.99
Maternal use of analgesics (opioid & non opioid)	20 (16.4)	9 (7.4)	0.03**
Maternal use of anti-emetics	28 (23)	14 (11.5)	0.01**
Maternal consumption of cured meat	9 (7.4)	4 (3.3)	0.15
Maternal use of hair spray	1 (0.8)	0 (0)	0.31
Maternal use of hair color	0 (0)	0 (0)	0.51
Maternal exposure to pesticides	0 (0)	1 (0.8)	0.31
Maternal vaginal infection	2 (1.6)	1 (0.8)	0.51
Maternal exposure to ultrasound	110 (90.2)	103 (84.4)	0.17
Maternal exposure to diagnostic X-ray	1 (0.8)	3 (2.5)	0.31
Maternal comorbidities			0.078
None	117 (95.9)	108 (88.5)	
Diabetes	1 (0.8)	2 (1.6)	
Hypertension	2 (1.6)	6 (4.9)	
Asthma/atopy	1 (0.8)	5 (4.1)	
Other	1 (0.8)	1 (0.8)	

*Significant at p value <0.05 by using Chi square or Fisher exact test.
**Significant at p value <0.05 by using independent t test or Mann Whitney U test.

data from high-income countries (HICs) reveals either no[18] or the opposite association,[10] the educational landscape in Pakistan differs significantly from HICs. Just over half the population in Pakistan attends school, with an average of less than 6 years of formal schooling.[19] Similar to economic status, educational background likely affects disease risk through a variety of factors, such as exposures, behavioral practices, ethnicity and race, disease-related awareness, and health-seeking behavior. These factors remain to be studied in the local context of Pakistan, and are an avenue inviting future investigation.

Limitations

Our study has several limitations. Firstly, being a single-center study, its data may not be generalizable to other centers across Pakistan. Secondly, as data were collected using a questionnaire, responses were prone to recall bias. Recall bias was mitigated by assessing exposure information from both cases and controls in a consistent manner. Thirdly, we anticipate reporting bias regarding maternal addictive use because addictive use and substance abuse are often stigmatized in many societies, including Pakistan. Women may face additional social and cultural stigma associated with substance use, leading to underreporting due to fear of judgment, shame, or negative consequences. Thirdly, while our study identified a three times higher risk of PBT with analgesic use, we were not able to explore the relationship for opioid and non-opioid analgesics separately and did not have sufficiently granular data to test a dose-response effect to strengthen causal inference. Nevertheless, our findings lay the ground for future detailed investigation into the risk conferred by different types of analgesics as well as the mechanisms involved in increasing risk.

Strengths

Our study has several strengths. Firstly, it is a matched case control study and matching on age and gender allowed the comparability of cases and controls in terms of these variables. This reduced the potential for bias due to these factors and strengthens the ability to attribute observed differences to the exposure of interest. Secondly, this is the first of its kind of study from our part of the world.

Table 4. Univariate and multivariable to determine independent socio-demographic and antenatal risk factors of PBTs in children and young people (CYP).

Variables	Unadjusted matched OR (95% CI)	Adjusted matched OR (95% CI)
Mother had any formal schooling	0.93 (0.9–1.02)*	NS
Father had no formal schooling	1.72 (0.8–3.6)*	NS
Paternal education*		
No education or primary	2 (1.2–4.6)	2.46 (1.09–5.55)**
Secondary and above	Reference	Reference
Father was not working	4 (1.1–14.2)*	NS
Number of family members (number of persons)	1.14 (1.04–1.2)*	NS
Household monthly income		
< Rs 40,000 ($198.8)/(€186.79)	Reference	Reference
Rs 40,000-80,000 ($198.8–397.6)/(€ 186.79–373.57)	0.9 (0.5–1.6)*	1.2 (0.6–2.3)
>Rs 80,000 (>$397.6)/(>€373.57)	1.3 (0.6–2.7)*	3.4 (1.1–10.2)**
Gestational age (weeks)	0.9 (0.72–1.07)*	NS
Birth Order		NS
3+	1.8 (0.9–3.5)*	
2	0.9 (0.5–1.7)	
1	Reference	
Mother's age at pregnancy (years)	0.9 (0.9–1.01)*	NS
Father's age at pregnancy (years)	0.9 (0.9–1.00)*	NS
Maternal use of analgesics	2.6 (1.07–6.2)*	3.0 (1.2–7.9)**
Maternal use of anti-emetics	2.9 (1.3–6.4)*	NS
Maternal consumption of cured meat	2.6 (0.7–10.0)*	NS
Maternal exposure to ultrasound	1.8 (0.8–3.9)*	NS
Paternal use of addictive substance/tobacco	11 (1.4–85.2)*	19.5 (2.1–179.8)**

*$p < 0.2$ on univariate regression.
**$p < 0.05$ on multivariable regression.

Conclusion

This matched case-control study, the first of its kind from Pakistan, found an association between maternal use of analgesics, paternal use of addictive substances, higher household income, and lower paternal education and primary brain tumors in children and young people which were robust to known potential confounders. Longitudinal multicenter studies will be required to test these associations prospectively

Clinical implications

Identifying these risk factors can help healthcare providers recognize children at higher risk, leading to early detection and timely treatment initiation. Moreover, knowledge of specific risk factors would enable healthcare providers to counsel expectant parents about the potential risks and empower them to make informed decisions regarding prenatal care. Understanding these risk factors can also contribute to development of strategies to minimize or avoid them during pregnancy, potentially reducing the incidence of brain tumors. Findings from the study can lead to the formulation of specific recommendations in prenatal care guidelines for brain tumor, enabling tailored care and early management of risk factors.

Patient and public involvement

This was a matched case control study design and the parents of cases and controls were interviewed via telephone by trained research assistants. The study findings will be disseminated to different stakeholders, such as healthcare professionals and cancer patients through: publications at local, national and international journals, presentations at conferences and workshops and through research briefs.

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Author contributions

NZ conceived the study, analyzed data, and critically reviewed the manuscript. SAE, TM and AM overlooked the study and critically reviewed the manuscript. FU and RSM revised, and critically reviewed the manuscript. FK collected the data. NM,

MM, NM, SA and SK critically reviewed the manuscript. NB overlooked the study and critically reviewed the manuscript.

Availability of data

Data will be available upon request from the corresponding author.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Ethical approval was obtained from the Aga Khan University ethics review committee. Ethical/institutional review committee AKU-ERC approval was obtained (ERC# 2020-4859-11855). Verbal consent was taken from the parents of the cases and controls after explaining the study procedure and its potential risks and benefits to them in Urdu or English as appropriate. All study materials containing personal identifiers were kept in a locked file cabinet. A unique study identification number was assigned to each participant. Data were entered in a password-protected electronic database that was only accessible to the research team.

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