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Grandpaternal Aging and the Risk of Primary Pediatric Brain Tumors in Grandchildren

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Abstract

Background and Aims: Previous research shows inconclusive evidence of a relationship between grandpaternal and parental aging and the risk of childhood brain tumors. This study aims to estimate the impact of advanced paternal and grandpaternal aging on the incidence of childhood brain tumors in Jordan.

Materials and Methods: This case-control study included pediatric primary brain tumor patients and controls, matched by age and gender, ascertained from the Jordanian Cancer Registry (JCR). Collected data included patients' diagnoses and birthdate, along with the ages of parents and paternal grandparents.

Results: The study included 183 pediatric brain tumor patients and 127 controls, matched by age and gender (p>0.05). Advanced grandpaternal age, defined as age at fathers' birth greater than 40 years, was present in 31.7% and 17.3% of cases and controls, respectively. Advanced grandpaternal age was associated with a 1.956-fold higher risk of developing all brain tumors (p=.012 (OR=1.956)). In participants with a grandpaternal age older than 30, advanced paternal age had a 6.56-fold increased risk of developing brain tumors (p=0.000, (OR=6.56)), an 8.4-fold increased risk of developing gliomas (p=.000, (OR=8.40)), a 4.1-fold increased risk of developing medulloblastomas (p=.045, (OR=4.1)). Grandpaternal age and advanced grandpaternal age were independent predictors for the incidence of all brain tumors, gliomas and medulloblastomas.

Conclusions : Advanced grandpaternal age or a combination of advanced grandpaternal and paternal age, when combined with other risk factors, may help prevent, screen, and aid in early detection of brain tumors in the pediatric population.

Keywords: Brain tumors; gliomas; medulloblastomas; pediatrics; advanced parental age; advanced grandpaternal age.

INTRODUCTION

Childhood brain tumors (CBTs) are primary brain tumors, either benign or malignant, that affect children and young adults before their 18th birthday [1]. These tumors represent the most common type of solid tumors in the pediatric population [2]. Their incidence is highly variable, with the highest incidence in the United States (5.14 per 100,000) [1]. Central nervous system tumours in Jordan represent 16.5% of childhood tumors, with a pediatric incidence of 2.09 per 100,000 for primary brain tumors [3, 4]. In past decades, both incidence and prevalence of CBTs increased due to advanced diagnostics and improved survival [2, 5]. The latter could be attributed to earlier diagnosis, advancements in neurosurgical techniques and multidisciplinary neuro-oncology, along with the identification of risk factors, such as ionizing radiation [6, 7]. Other risk factors - some are still debatable - are cancer syndromes (Neurofibromatosis type 1; Neurofibromatosis Type 2; tuberous sclerosis; Li-Fraumeni syndrome and hereditary retinoblastoma); familial history; lack of early infection exposure; congenital anomalies; advanced parental age; higher birth weight; increased head circumference at birth; and maternal medications [8-15].

For instance, the use of CT scan to deliver a cumulative dose of 60 mGy tripled the risk of primary pediatric brain tumors [16]. Regarding infection exposure, children of mothers who had a documented viral infection during pregnancy had an 11-fold increased risk of a malignant nervous system tumor [17]. In support, Krynska et al. reported JCV DNA positivity in 11 of 23 medulloblastoma samples [18]. Birth anomalies were also associated with a higher risk for medulloblastomas [19]. Regarding maternal medications, antihypertensives, such as beta-blockers, diuretics, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers were associated with an increased risk of brain tumors in offspring [20].

One of the inconsistent factors among these is parental age [21]. Established associations between advanced paternal age and sporadic achondroplasia and Apert syndrome, along with advanced maternal age and Down Syndrome are documented [22-24]. In the context of tumors, a Korean case-control study found that paternal age >40 results in earlier onset of breast cancer and increases a daughter's lifetime incidence of breast cancer with 1 in 5.3 compared to 1 in 8.5 if the father's age was <30 [25]. In childhood tumors, a 1.5 relative risk for developing childhood leukemia was found among children of men aged 35 or older [26]. However, inconsistent findings exist regarding the association between advanced paternal age and childhood brain tumors [9, 27-32]. On the affirmative side, investigators from Sweden demonstrated a 25% increased risk of brain tumors in children born to fathers over 30 compared to those younger than 25, a risk that held significant when adjusting for maternal age [9]. Another population-based Swedish study illustrated a significant effect for paternal age over childhood central nervous system cancer and astrocytoma risk when maternal age was included in the analysis [31]. Similarly, the mean neurofibromatosis type 1 (Cancer syndrome) sporadic case paternal age at birth was 32.0 years compared with 28.8 years in the general population of the Czech Republic [28]. Increased risk of childhood CNS tumors was also observed for a 5-year increase in maternal and paternal ages in Californians with a specific increased risk of astrocytoma for a 5-year increase in paternal age [29]. Inconsistent with these findings, a Peruvian case-control study found no association between advanced paternal age and development of childhood brain tumors, except for retinoblastoma in

shared parental aging [27]. Similarly, a Danish population-based registry study revealed no associations regarding advanced paternal age and childhood brain tumors [32]. Due to inconsistency and lack of regional and local studies, this study aimed to evaluate the impact of advanced paternal and grandpaternal aging on the incidence of childhood brain tumors in Jordan.

MATERIAL AND METHODS

Study Structure

This study is a case-control study that included 183 pediatric primary brain tumor patients and 127 controls. All cases were ascertained from Jordan University Hospital (JUH) records and Jordanian Cancer Registry (JCR). Controls were matched parallel to case age and gender and acquired from JUH medical records, with exclusion for all patients with personal history of tumors or familial history of brain tumors. Inclusion criteria included living and deceased patients with a histologically confirmed diagnosis of a primary brain tumor, either benign or malignant, before their 18th birthday. Through using available records and calling guardians, familial history of brain tumors or syndromes, histopathological tumor type, outcome (alive or dead), and birth dates of child, parents and grandparents were obtained.

Ethical approval and participant consent

Ethical approvals were obtained from the Academic Research Council of the Faculty of Medicine at the University of Jordan and the Institutional Review Board in the Ministry of Health, in accord with the ethical principles of the Helsinki Declaration. Verbal consent was obtained from all parents/legal guardians, as approved by the Academic Research Council of the Faculty of Medicine at the University of Jordan. (Written consent was not acquired due to fear of SARS-COV2 contact).

Statistical Analysis

Data was entered into a spreadsheet and analyzed using the IBM SPSS Statistics for Windows, version 22 (IBM Corp, Armonk, NY, USA). Descriptive statistics obtained included the mean and standard deviation for each variable measured. An Independent T-test was used to investigate the relationship between child, paternal, maternal and grandpaternal age and brain tumor incidence and outcome. Chi-square and odds ratio analysis was performed to evaluate the relationship between gender, advanced paternal, maternal and grandpaternal age, and age subgroups and brain tumors incidence and outcome. Significance level was set at 0.05.

RESULTS

Cases and Controls' Characteristics

Our case-control included 183 primary brain tumor patients diagnosed before their 18th birthday and 127 tumor-free controls with no familial history of brain tumors. Age and gender were matched, as evident in age mean and standard deviation (9.35 (SD=4.11) in primary brain tumors patients vs 9.83 (SD=4.92) in controls, p=.794) and gender distribution (62.8% (115) males and 37.2% (68) females in primary brain tumors patients vs 61.4% (78) males and 38.6% (49)). For cases and controls, respectively, the average paternal age at birth, maternal age at birth, and grandpaternal age at father's birth were (33.98 (SD=7.34) vs 33.87 (SD=6.18), P=.893), (27.25 (SD=5.95) vs 28.18 (SD=5.61), P=.167) and (27.19 (SD=5.96) vs 33.85 (SD=11.83), P=.000), respectively. (See Table 1).

Most primary pediatric brain tumors patients were diagnosed with gliomas

(55.2%) or medulloblastomas (39.3%). Table 2 shows the distribution of specific diagnoses according to the International Classification of Diseases (ICD). The most common location for brain tumors was the cerebellum (37.2%), followed by the brain stem (14.2%) and cerebrum (7.1%). More than 80% of these patients were still alive, with 16.9% being deceased.

Table 1: Characteristics of children diagnosed with primary brain tumors and controls (2002-2018).

Characteristics	Cases *(183)* *n (%)*	Controls *(127)* *n (%)*	*p*-value (Odds Ratio)
Sex			.813 (1.062)
Male	115 (62.8)	78 (61.4)	
Female	68 (37.2)	49 (38.6)	
Age at Diagnosis			.794
Mean (Standard Deviation)	9.35 (4.11)	9.83 (4.92)	
Paternal Age at Birth			.893
Mean (Standard Deviation)	33.98 (7.34)	33.87 (6.18)	
Advanced Paternal Age (>40)	24 (13.1)	18 (14.2)	.866 (.906)
20-25	17 (9.3)	8 (6.3)	
26-30	42 (23)	33 (26)	
31-35	65 (35.5)	36 (28.3)	
36-40	35 (19.1)	31 (24.4)	
41-45	13 (7.1)	17 (13.4)	
46-50	7 (3.8)	0 (0)	
> 51	4 (2.2)	2 (1.6)	
Maternal Age at Birth			.167
Mean (Standard Deviation)	27.25 (5.95)	28.18 (5.61)	
Advanced Maternal Age (>40)	4 (2.2)	3 (2.4)	1.000 (1.100)
16-20	21 (11.5)	8 (6.3)	
21-25	53 (29)	36 (28.3)	
26-30	62 (33.9)	40 (31.5)	
31-35	27 (14.8)	27 (21.3)	
36-40	16 (8.7)	10 (7.9)	
41-	4 (2.2)	3 (2.4)	

Paternal-Maternal age gap			.193
Mean (Standard Deviation)	6.32 (5.00)	5.64 (4.15)	
Grandpaternal age at father's birth			**.000**
Advanced Grandpaternal Age (>40)	58 (31.7)	22 (17.3)	**.012 (1.956)**
Mean (Standard Deviation)	27.19 (5.96)	33.85 (11.83)	
10-25	24 (13.1)	20 (15.7)	
26-30	36 (19.7)	38 (29.9)	
31-35	31 (16.9)	20 (15.7)	
36-40	32 (17.5)	14 (11)	
41-45	19 (10.4)	11 (8.7)	
46-50	11 (6)	7 (5.5)	
> 51	25 (13.7)	4 (3.1)	

Table 2: Diagnoses in 183 primary brain tumors patients

Variable	Cases	Variable	Cases
Diagnoses		Anaplastic Oligodendroglioma	1 (0.5)
Glioma	101 (55.2)	Medulloblastoma, NOS	51 (27.9)
Medulloblastoma	72 (39.3)	Desmoplastic nodular medulloblastoma	16 (8.7)
Others	10 (5.5)	Primitive neuroectodermal tumor, NOS	6 (3.3)
Specific diagnosis (in accord to ICD codes)		Large cell medulloblastoma	5 (2.7)
Glioma, Malignant	27 (14.8)	**Status**	
Gliomatosis cerebri	1 (0.5)	Living	152 (83.1)
Mixed Glioma	4 (2.2)	Dead	31 (16.9)
Choroid Plexus Carcinoma	3 (1.6)	**Tumor Location**	
Astrocytoma, NOS	14 (7.7)	Cerebrum	13 (7.1)
Anaplastic Astrocytoma	7 (3.8)	Frontal Lobe	7 (3.8)
Fibrillary astrocytoma	16 (8.7)	Temporal Lobe	7 (3.8)
Polar spongioblastoma	1 (0.5)	Parietal Lobe	5 (2.7)
Pleomorphic xanthoastrocytoma	1 (0.5)	Ventricles, NOS	7 (3.8)
Glioblastoma, NOS	26 (14.2)	Cerebellum, NOS	68 (37.2)
Gliosarcoma	2 (1.1)	Brain Stem	26 (14.2)
Oligodendroglioma, NOS	2 (1.1)	Unspecified in Brain	50 (27.3)

The effect of paternal age on brain tumors risk in offspring

The majority of cases and controls had a paternal age at birth between 31 and 35 (35.5% vs 28.3%, respectively, *p*=.893). Independent T-test revealed insignificant effect for the paternal-maternal age gap over the overall brain tumors risk, the specific risk for gliomas and medulloblastomas or specific locations, and brain tumor patient outcomes (*p*>0.05). Advanced paternal age, as defined for age at birth greater than 40 years, was present in 13.1% and 14.2% of cases and controls, respectively, *p*=.866 (OR=.906). (See Table 1). Paternal age and advanced paternal age had an insignificant effect on the overall brain tumor risk, the specific risk for gliomas and medulloblastomas or specific locations, and brain tumor patients' outcomes (*p*>0.05). No significant difference was present between glioma and medulloblastoma patients.

The effect of maternal age on brain tumors risk in offspring

The majority of cases and controls had a maternal age at birth between 26 and 30 (33.9% vs 31.5%, respectively, *p*=.167). Advanced maternal age, as defined by age at birth greater than 40 years, was present in 2.2% and 2.4% of cases and controls, respectively, *p*=1.000 (OR=1.100) (See Table 1). Maternal age and advanced maternal age had an insignificant effect on overall brain tumor risk, specific risk for gliomas and medulloblastomas or specific locations, and brain tumor patient outcomes (*p*>0.05). No significant difference was present between glioma and medulloblastoma patients.

The effect of paternal-maternal age gap on brain tumors risk in offspring

The mean paternal-maternal age gap was 6.32 (SD=5.00) and 5.64 (SD=4.15), respectively (P=.193) (See Table 1). Independent T-test revealed insignificant effect for the paternal-maternal age gap over the overall brain tumor risk, the specific risk for gliomas and medulloblastomas or specific locations, and brain tumor patient outcomes (*p*>0.05). No significant difference was present between glioma and medulloblastoma patients.

The effect of grandpaternal age on brain tumors risk in offspring

The majority of cases and controls had a grandpaternal age at fathers' birth between 26 and 30 (19.7% vs 29.9% respectively, *p*=.000) (See Table 1). Mean comparison showed a significant difference between cases and controls (27.19 (SD=5.96) vs 33.85 (SD=11.83), *p*=.000). When compared to controls (33.85 (SD=11.83)), significant mean differences were also found in glioma patients (27.43 (SD=6.17)) and medulloblastoma patients (27.08 (SD=5.77)). However, no significant differences were found between gliomas and medulloblastomas patients (*p*=.703).

Advanced grandpaternal age, defined by age at fathers' birth greater than 40 years, was present in 31.7% and 17.3% of cases and controls, respectively. Advanced grandpaternal age correlated with overall brain tumor risk (*p*=.012 (OR=1.956)) and medulloblastoma risk (*p*=.003, (OR=2.66)), but not gliomas risk (*p*=.147, (OR=.1.62), the outcome of all brain tumor patient outcomes (*p*=.291, (OR=1.749)), medulloblastoma patients (*p*=1.000, (OR=1.316)), and glioma patients (*p*=.415, (OR=1.855)), and tumor location (*p*=.279). Oppositely, a cut-off of 30 years conferred a protective trend (*p*=.000, (OR=316)). No significant differences were found between gliomas and medulloblastomas patients.

The effect of combined aging on brain tumors risk in offspring

When only including cases and controls

with a paternal age older than 30, participants with advanced grandpaternal age had a 2.46-fold increased risk of developing brain tumors (p=0.006, (OR=2.46)); 2.39-fold increased risk of developing gliomas (p=.019, (OR=2.39)); 2.95-fold increased risk of developing medulloblastomas (p=.007, (OR=2.95)) and no effect over the outcome of all primary brain tumors patients, glioma patients and medulloblastoma patients (p>0.05). Advanced maternal and paternal age had an insignificant effect on all of these risks (p>0.05). No significant differences were found between gliomas and medulloblastomas patients.

When only including cases and controls with a maternal age older than 30, participants with advanced grandpaternal age had a 6.54-fold increased risk of developing brain tumors (p=0.001, (OR=6.54)); a 6.8-fold increased risk of developing gliomas (p=.002, (OR=6.8)); 7.58-fold increased risk of developing medulloblastomas (P=.005, (OR=6.8)); and no effect over the outcome of all primary brain tumors patients, glioma patients and medulloblastoma patients (p>0.05). Advanced maternal and paternal age had an insignificant effect on all of these risks (p>0.05). No significant differences were found between gliomas and medulloblastomas patients.

When only including cases and controls with a grandpaternal age older than 30, participants with advanced paternal age had a 6.56-fold increased risk of developing brain tumors (p=0.000, (OR=6.56)); an 8.4-fold increased risk of developing gliomas (p=.000, (OR=8.40); a 4.1-fold increased risk of developing medulloblastomas (p=.045, (OR=4.1); but not the outcome of all primary brain tumor patients, glioma patients and medulloblastoma patients (p>0.05). Advanced maternal and grandpaternal age had an insignificant effect on all of these risks. No significant differences were found between gliomas and medulloblastomas patients.

Binomial logistic regression analysis of all ages revealed grandpaternal age at fathers' birth and advanced grandpaternal age as independent predictors of all brain tumors, gliomas and medulloblastomas incidences (p<0.05).

DISCUSSION

This work represents the first published study focused on the elemental and combinatory effect of advanced grandpaternal and parental (maternal or paternal age) age as risk factors for primary brain tumors in children.

Advanced parental aging (APA), defined as age older than 40 at the birth of offspring, has been frequently linked to many diseases, including neurodevelopmental disorders, such as autism spectrum disorder (ASD); schizophrenia; Down syndrome; musculoskeletal syndromes and neoplasms [33]. The latter include acute lymphoblastic leukemia, non-Hodgkin lymphoma, gonadal germ cell tumors, retinoblastoma and brain cancers [9, 33]. The incidence of pediatric solid tumors is on the rise, with brain tumors increasing from 1973 to 2008 then plateauing [34]. The mechanism behind advanced parental aging-mediated predisposition to cancers in offspring is still mostly unknown. One theory centres around increased chromosomal abnormalities and genetic aberrations in germ cells with aging. An APA model in mice supported this theory, as epigenetical alterations in insulin receptor signalling genes, immune system signalling and brain development genes occurred [35]. This model revealed a transgenerational effect, in which advanced grandpaternal age altered the epigenetics mentioned above [35].

Other theories include changes in hormonal levels in the female reproductive system.

In our case-control study, no effect was found for advanced parental age, paternal or maternal, over the risk for all brain tumors, gliomas and medulloblastomas, along with their outcome. These results were similar to a Peruvian study that illustrated a lack of relationship between childhood brain tumors and advanced paternal age [27]. However, our results contraindicated findings from a Californian study, in which an increased risk for childhood CNS tumors was observed for a 5-year increase in maternal and paternal ages [29]. Our study also contraindicated this, as advanced maternal age and the paternal-maternal age gap did not affect all primary brain tumors' risk and outcome. Interestingly, analysis including grandchildren of grandfathers older than 30 at the delivery of the fathers' generation revealed a risk-increasing effect for advanced paternal age of 6.56-fold for all primary brain tumors, 8.4-fold for gliomas and 4.1-fold for medulloblastomas. To the best of our knowledge, this synergistic effect was not described in previous literature.

Moreover, advanced grandpaternal age, defined as grandparent age older than 40 at the father's delivery, increased overall brain tumors risk (OR=1.956) and medulloblastoma risk (OR=2.66) but not gliomas. These risks were even higher and included gliomas when advanced grandpaternal age was combined with paternal or maternal age older than 30. The effects of grandpaternal age were also supported by logistic regression analysis, which identified grandpaternal age and advanced grandpaternal age as independent predictors of all primary brain tumors, gliomas and medulloblastomas. To the best of our knowledge, the effect of grandpaternal aging on primary pediatric brain tumors was not investigated before our study.

The findings of this study, when combined with other identified risk factors such as exposure to ionizing radiation, may help in setting educational screening programs that aid in preventing brain tumors while enhancing early detection and intervention. However, due to its observational nature, our case-control presents with strengths and weaknesses. One of the main strengths is being the first study to evaluate the effects of advanced parental aging on primary pediatric brain tumors in Jordan and the region and the first to determine the relationship between advanced grandpaternal age and primary pediatric brain tumors. On the other hand, the main weakness of our study is the small sample size and the lack of more detailed outcomes, and the lack of exclusion for possible risk factors, except for tumor syndromes. Accordingly, we recommend larger sample sizes, more consideration of confounding factors and the investigation of paternal and grandpaternal exposures and diseases to find their role in aging-mediated changes. We also recommend performing experimental studies to establish the relationship between grandpaternal and parental aging on primary pediatric brain tumors and possible molecular pathways and targets.

CONCLUSION

Our case-control study aimed to determine the effect of parental and grandpaternal aging on primary pediatric brain tumors risk and outcome. Our analysis revealed an independent effect for grandpaternal age on all primary brain tumors, gliomas and medulloblastomas. Moreover, a combination of grandpaternal and paternal aging was associated with a greater risk for primary pediatric brain tumors in the third generation.

The findings of this study, when combined with other identified risk factors such as exposure to ionizing radiation, may help in setting educational screening programs, aiding in preventing brain tumors, while enhancing early detection and intervention. In addition, our results emphasize the need for experimental studies to establish the relationship between grandpaternal and parental aging on primary pediatric brain tumors and possible molecular pathways and targets for prevention, detection, and treatment.

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The authors declare no conflict of interest

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شيخوخة الجد وخطر الإصابة بأورام دماغ الأطفال الأولية لدى الأحفاد

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الملخص

الخلفية والأهداف: تشير الأبحاث السابقة إلى وجود أدلة غير محتملة على العلاقة بين شيخوخة الجدود والآباء واحتمالية الإصابة بأورام الدماغ في الأطفال. يهدف بحثنا إلى تقدير تأثير شيخوخة الآباء والجدود على انتشار أورام الدماغ في الأطفال في الأردن.

منهجية الدراسة: شملت دراستنا حالات أورام الدماغ الأولية في الأطفال ومجموعات مرجعية متطابقة من حيث العمر والجنس، تم التحقق منها من سجل الأورام الأردني. المعلومات المجموعة شملت تشخيص الطفل وتواريخ ميلاد المريض ووالديه والجدود من جهة الأب.

النتائج: شملت دراستنا 183 حالة من مرضى أورام الدماغ في الأطفال و 127 حالة مرجعية متطابقة من حيث العمر والجنس .(P>0.05) وجد أن شيخوخة الجدود المتقدمة، والتي تعرف بأن عمر الجد حين ولادة الأباء عند يزيد عن 40 عامًا، كانت موجودة في 31.7٪ و 17.3٪ من الحالات والمراجعين على التوالي. كانت شيخوخة الجدود المتقدمة مرتبطة بارتفاع مقداره 1.956 في احتمالية تطوير جميع أنواع أورام الدماغ .((OR=1.956) P=0.012) فيما يتعلق بالمشاركين الذين تجاوز عمر الأجداد الستين عامًا، كانت شيخوخة الآباء المتقدمة تزيد احتمالية تطوير أورام الدماغ بنسبة 6.56 مرة(P=0.000 ، ((OR=6.56)، وتزيد احتمالية تطوير الأورام الدبقية بنسبة 8.4 مرة(P=0.000 ، ((OR=8.40)، وتزيد احتمالية تطوير أورام الأورمية النخاعية بنسبة 4.1 مرة(P=0.045 ، .((OR=4.1))كانت شيخوخة الجدود وشيخوخة الجدود المتقدمة تعتبر توقعات مستقلة لانتشار جميع أنواع أورام الدماغ والأورام الدبقية والأورام الأورمية النخاعية.

الاستنتاجات: يمكن أن تساهم شيخوخة الجدود المتقدمة أو مجموعة من شيخوخة الجدود والآباء المتقدمة، عند مشاركتها مع عوامل الخطر الأخرى، في تعزيز الوقاية والفحص والكشف المبكر عن أورام الدماغ في السكان الأطفال.

الكلمات الدالة: أورام الدماغ؛ الأورام الدبقية؛ الأورام الأورمية النخاعية؛ طب الأطفال؛ شيخوخة الآباء.