The effect of parental age on NF1 patients in Turkey

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Abstract Neurofibromatosis type 1 (NF1) is the most common neurogenetic disorder worldwide, and its clinical presentations are highly variable. NF1 is caused by mutations in the *NF1* gene, and 50% of NF1 cases are sporadic, which occur in the absence of a family history of the disease and usually result from a new mutation in the germline of a parent. Advanced paternal age may increase the risk for germinal *NF1* mutations; however, some dominant conditions, including neurofibromatosis, have shown a lesser association with paternal age, although there are conflicting reports in the literature. We investigated the effects of paternal and maternal age in 241 NF1 patients (121 sporadic and 120 familial cases) who were seen in Hacettepe hospital, a reference center for genetic diseases in Turkey. For statistical analysis, Spearman's and Chi-square tests were used. In this study, we evaluated paternal and maternal age at birth in sporadic and familial cases of NF1. We also compared the effect of parental age on the appearance and coexistence of various NF1 symptoms. There were no significant statistical differences between paternal age and coexistence of the NF1 symptoms. However, a slightly negative

correlation was observed between paternal age and the coexistence of NF1 symptoms in familial cases ($p < 0.05$). We did not find strong evidence for the effect of parental age on the clinical severity of NF1.

Keywords Neurofibromatosis type 1 · Advanced paternal age · Advanced maternal age · Spontaneous mutations

Introduction

Neurofibromatosis type 1 (NF1) is the most common neurogenetic disorder which affects 1 in 3000–3500 individuals worldwide (Rasmussen and Friedman 2000). The clinical presentation of NF1 is highly variable (Friedman 1999; Williams et al. 2009); some typical appearances are cafe-au lait spots, frecklings, malignant peripheral nerve sheath tumors (MPNST; neurofibromas as a benign form and neurofibrosarcomas as a malignant form), and other malignancies, such as intracranial astrocytomas, gastrointestinal stromal tumors, pheochromocytoma,

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mas, and juvenile monocytic leukemia (Ferner et al. 2007; Theos et al. 2006). Other manifestations that occur less frequently are endocrine symptoms and neurological and ophthalmological problems (Ferner et al. 2007).

The *NF1* gene (MIM #162200) is one of the largest human genes (~350 kb) and is located at 17q11.2. The *NF1* gene encodes the neurofibromin protein, which is a negative regulator of the Ras oncogene (Rasmussen and Friedman 2000). The disease NF1 is caused by mutations in the *NF1* gene, and 50% of NF1 cases are sporadic. Sporadic cases occur in the absence of a family history of the disease and usually result from a de novo mutation in the germline of a parent. It has been reported that there are families in which more than one sporadic cases are observed, each with a distinct *NF1* mutation (Klose et al. 1999; Upadhyaya et al. 2003). Moreover, parental mosaicism for an *NF1* mutation, including a germline mutation, can also be considered as a sporadic case (Detjen et al. 2007; Kaplan et al. 2010).

As the living conditions in developed countries change (educationally, financially, etc.), the marriage age and health consciousness have increased. Many studies have shown that the development of congenital syndromes, as well as those that predispose to cancer, are associated with advanced maternal age (AMA) and advanced paternal age (APA) (Crow 2000). The average age of parents at the time of conception varies among countries by 1 or 2 years. However, conception at the age of >35 for mothers and >40 for fathers is considered as advanced parental age (Friedman 1981; Snajderova et al. 2012; Toriello et al. 2008).

It has been shown that the mutation rate for base substitutions is much higher in men than in women as the age of conception increases (Crow 2006; Ittel et al. 1975; Risch et al. 1987). There is also some evidence that increased risk for complex disorders, including some congenital anomalies, schizophrenia, autism spectrum disorders, bipolar disorder, autism, and childhood cancers, is associated with APA (Byrne et al. 2003; Cantor et al. 2007; Dalman and Allebeck 2002). However, there is no information on the relationship between APA and aneuploidy or structural chromosome abnormalities; the exceptions are trisomy 21 and Klinefelter syndrome. APA could have an effect either alone or together with AMA (Fisch et al. 2003; Shi and Martin 2000).

One of the suggested mechanisms underlying the increased risk of new gene mutations in older males during spermatogenesis is replication errors (due to the large number of cell divisions during spermatogenesis) and reduced activity of repair enzymes (Crow 2000). Another possible mechanism is related to the methylation of human sperm DNA. According to Glaser and Jabs (2004), the methylation rate of sperm DNA, especially at CpG dinucleotides, is much higher than that of oocyte DNA, which in turn greatly increases the risk of point mutations occurring within a CpG dinucleotide in sperm DNA (Glaser and Jabs 2004). Goriely and Wilkie (2012) suggested a mechanism in which these mutations are selected. These selected mutations are then expanded in the testes, resulting in enrichment of mutant sperm over time. They hypothesized that this dysregulation of spermatogonial cell

Table 1 The mean of parental age for sporadic and familial cases

	N	Min (age)	Max (age)	Mean ± SD
Sporadic Cases:				
- Age of a mother at the time of conception	119	16	45	27.04 ± 6.4
- Age of a father at the time of conception	120	20	62	31.82 ± 7.2
- Age of patient at the time of diagnosis	121	1	56	11.83 ± 9.9
Familial Cases:				
- Age of a mother at the time of conception	118	17	40	27.19 ± 5.3
- Age of a father at the time of conception	118	19	52	31.58 ± 6.2
- Age of patient at the time of diagnosis	120	1	55	11.81 ± 10.5

function occurred through the growth factor receptor-RAS signal transduction pathway (Goriely and Wilkie 2012).

APA may increase the risk for new germinal *NF1* mutations. In previous studies, it was shown that the risk of having a child with neurofibromatosis is 1:810–1:1080 among fathers aged > 50 years (Risch et al. 1987) and 1:1034–1:1380 among fathers aged > 40 years (Bunin et al. 1997). Some dominant conditions, including NF1, showed a lesser association with paternal age, although there are conflicting reports on this subject (Liu et al. 2015; Snajderova et al. 2012). Although most studies have shown an effect of APA on de novo mutations, some previous studies pointed out that certain types of mutations, like *NF1* microdeletions, are passed on from the maternal germline in sporadic cases (Lazaro et al. 1996). For this reason, the effect of maternal age cannot be ignored in the development of de novo NF1 cases. However, whether AMA has an effect on de novo mutations is still unknown (Liu et al. 2015).

In this study, we aimed to assess the effect of parental age on the incidence of NF1 and the coexistence of different NF1 symptoms in a Turkish population.

Materials and methods

NF1 patients

We assessed paternal and maternal age of 241 patients with NF1 (121 sporadic and 120 familial cases) who were admitted

Table 2 The correlation coefficient between the presence of tumors and the parental age

	Maternal age	Paternal age
Sporadic	0.058 ($p > 0.5$)	0.126 ($p > 0.1$)
Familial	0.161 ($p > 0.1$)	0.043 ($p > 0.01$)

to Hacettepe hospital, Ankara, which is a reference center for genetic diseases in Turkey, between 1999 and 2014. Patients were diagnosed with NF1 according to the National Institutes of Health NF1 (NIH-NF1) clinical criteria (DeBella et al., 2000; Ferner et al. 2007). Sporadic cases were diagnosed by preparing and consulting detailed pedigree information together with a lack of parental signs of NF1. The clinical and genetic analyses were performed according to the guidelines in the Declaration of Helsinki and approved by the ethical committee of Hacettepe University, Turkey.

Turkish population

Data related to maternal and paternal ages of the Turkish population were obtained from the Turkish Ministry of Health and Statistical Institute database.

Clinical data

Detailed information about the clinical findings of the patients was obtained by using a questionnaire, which was prospectively filled out either by a dermatologist, pediatric neurologist, or clinical geneticist. The questionnaire included the clinical features of NF1, including tumors and other neurological problems. Clinical data was stored in our in-house developed database.

Ethical compliance

The study was approved by the ethics review board of Hacettepe University, Faculty of Medicine.

Statistical analysis

Data are expressed as mean $\pm$ SD or percentage, as appropriate. The chi-square (χ^2) test was used to compare distributions between groups. Spearman's rho test was used to determine bivariate correlations between selected variables. Correction for multiple testing of coexistence of symptoms was performed using the Benjamini-Hochberg method (Benjamini and Hochberg 1995). Statistical analyses were performed by using a commercially available statistical software package (PASW Statistics, Release 18.0).

Results

We retrospectively evaluated the medical records of 241 patients with NF1 (121 sporadic and 120 familial cases). The percentages of females among the sporadic and familial cases were 55.4% (67/121) and 51.70% (62/120), respectively. The mean parental age is shown in Table 1. The correlation between maternal/paternal age and the presence of tumors in the

Table 3 The percentage of clinical features distributed among the maternal age subgroups, both in sporadic and familial cases

Groups of maternal age						
	Sporadic cases (%)			Familial cases (%)		
	< 25 years old (n = 56)	26–34 years old (n = 51)	> 35 years old (n = 12)	< 25 years old (n = 43)	26–34 years old (n = 63)	> 35 years old (n = 8)
Café-au-lait spots	96.4	96.1	91.7	91.5	95.2	100.0
Axillary freckling	55.4	60.8	58.3	66.0	52.4	25.0
Inguinal freckling	32.1	27.5	25.0	34.0	30.2	12.5
Lisch nodules	37.5	27.5	66.7	29.8	19.0	50.0
Cutaneous neurofibroma	37.5	23.5	33.3	29.8	27.0	0.0
Plexiform neurofibroma	16.1	9.8	16.7	21.3	15.9	0.0
Optic glioma	14.3	15.7	33.3	12.8	23.8	25.0
Skeletal dysplasia	28.6	13.7	8.3	31.9	20.6	12.5
Astrocytoma	1.8	2.0	0.0	0.0	1.6	0.0
Hamartoma	5.4	3.9	0.0	2.1	9.5	12.5
Rhabdomyosarcoma	0.0	3.9	0.0	0.0	0.0	12.5
Epilepsy	3.6	3.9	0.0	4.3	0.0	0.0
Hypertension	5.4	2.0	0.0	0.0	1.6	0.0
Learning disability	1.8	2.0	8.3	4.3	4.8	0.0
MPNST	3.6	2.0	0.0	0.0	1.6	0.0
Scoliosis	7.1	0.0	8.3	2.1	9.5	0.0

Table 4 The percentage of clinical features distributed among the paternal age subgroups, both in sporadic and familial cases

Groups of paternal age (sporadic cases)						
	Sporadic cases (%)			Familial cases (%)		
	< 25 years old (n = 21)	26–39 years old (n = 88)	≥ 40 years old (n = 11)	< 25 years old (n = 16)	26–39 years old (n = 93)	≥ 40 years old (n = 9)
Café-au-lait spots	95.2	96.6	100.0	93.5	93.5	100.0
Axillary freckling	38.1	64.8	54.5	81.3	53.8	44.4
Inguinal freckling	23.8	31.8	27.3	25.0	32.3	22.2
Lisch nodules	28.6	34.1	72.7	43.8	21.5	33.3
Cutaneous neurofibroma	28.6	33.0	18.2	31.3	26.9	22.2
Plexiform neurofibroma	14.3	12.5	9.1	25.0	16.1	0.0
Optic glioma	23.8	12.5	36.4	12.5	17.2	55.6
Skeletal dysplasia	28.6	20.5	0.0	56.3	20.4	11.1
Astrocytoma	4.8	1.1	0.0	0.0	1.1	0.0
Hamartoma	0.0	5.7	0.0	6.3	7.5	0.0
Rhabdomyosarcoma	0.0	2.3	0.0	0.0	1.1	0.0
Epilepsy	0.0	4.5	0.0	6.3	1.1	0.0
Hypertension	4.8	3.4	0.0	0.0	1.1	0.0
Learning disability	0.0	3.4	0.0	6.3	4.3	0.0
MPNST	4.8	2.3	0.0	0.0	1.1	0.0
Scoliosis	9.5	3.4	0.0	6.3	6.5	0.0

NF1 patients was examined and no correlation was observed (Table 2).

According to the Turkish Ministry of Health and Statistical Institute database, the mean maternal age at birth in Turkey is 28.8 ± 5.8 years and the mean paternal age is 32.5 ± 6.5 years. In this study, advanced parental age at conception was defined

as father's age ≥ 40 years and a mother's age > 35 years (Friedman 1981).

Based on Turkish Statistical Institute data, the mean parental age at first birth in Turkey is 22.3 years. Therefore, we analyzed the data by placing patients in three different subgroups based on maternal and paternal age (maternal age < 25 ,

Table 5 The correlation coefficient between the parental age and the appearance of the NF1 symptoms of sporadic cases

	Maternal age at time of conception	Paternal age at time of conception
Café-au-lait spots	−0.053	0.01
Axillary freckling	0.052	0.09
Inguinal freckling	−0.027	0.016
Lisch Nodules	−0.02	0.099
Cutaneous neurofibroma	−0.128	−0.016
Plexiform neurofibroma	−0.045	−0.022
Optic Glioma	0.095	0.056
Skeletal dysplasia	−0.206*	−0.099
Astrocytoma	−0.007	−0.041
Hamartoma	−0.092	−0.061
Rhabdomyosarcoma	0.142	0.136
Epilepsy	−0.042	0.006
Hypertension	−0.072	−0.038
Learning disability	0.113	0.028
MPNST	−0.034	−0.098
Scoliosis	0.605	0.546

**p* value is ≤ 0.05 and considered as statistically significant

Table 6 The correlation coefficient of coexistence of the symptoms of NF1 (p value of ≤ 0.05 is considered as statistically significant) in sporadic cases

Coexistence of the symptoms	Correlation Coefficient	Significance*
Learning disability and hamartoma	0.234	$p < 0.01$
Hypertension and hamartoma	0.194	$p < 0.05^{**}$
MPNST and skeletal dysplasia	0.187	$p < 0.05^{**}$
MPNST and plexiform neurofibroma	0.252	$p < 0.005$
Inguinal freckling and axillary freckling	0.509	$p < 0.001$

*The p values are not corrected for multiple testing

**Not significant after correction for multiple testing

26–34, > 35 years; paternal age <25, 26–39, ≥ 40 years). The distributions of the clinical features of patients with sporadic and familial NF1 are shown by maternal and paternal subgroups in Table 3 and Table 4, respectively. The correlations between parental age and clinical symptoms were assessed. A negative correlation between maternal age and the presence of skeletal dysplasia ($p \leq 0.05$) was observed (Table 5). Similarly, the coexistence of symptoms was also analyzed, and the co-occurrence of some clinical features was statistically significant (Table 6). The relation between the sex of the patients and NF1 symptoms were also analyzed; however, no relation was detected.

Conclusion

In the majority of previous studies (Dubov et al. 2016; Liu et al. 2015), the average age of fathers of children with sporadic NF1 at birth was higher than that of fathers of normal children in the general population. In contrast, no evidence of a strong effect of maternal age in sporadic NF1 has been reported. However, in the present study, the average age of fathers at conception of children with sporadic NF1 was 31.82 ± 7.2 years, and that of the mothers was 27.04 ± 6.4 years; both of which are lower than the mean maternal and paternal ages for normal births in Turkey (28.8 ± 5.8 and 32.5 ± 6.5 years, respectively). This could be due to the high rate of consanguineous marriage at young ages, which is common in Turkey. Consequently, we did not find strong evidence for a parental age effect on the risk of NF1 in offspring.

Next, we tested for correlations between the symptoms of NF1 and parental age at conception. We detected a negative correlation between maternal age at conception and the appearance of skeletal dysplasia ($p < 0.05$) in sporadic cases but not in familial cases. In addition, some significant correlations between the coexistence of clinical features were detected. The co-occurrence of inguinal freckling and axillary freckling was observed, as expected ($p < 0.001$). This correlation was also reported before (Szudek et al. 2003). Statistically significant associations between the coexistence of MPNST and skeletal dysplasia, hypertension and hamartoma, and learning disability and hamartoma, were observed for the first

time in this study albeit observed correlations between MPNST and skeletal dysplasia, and hypertension and hamartoma did not survive multiple testing correction. The correlation between these clinical features may lead to some insight into the modifier genes and cross talk between cellular pathways. The coexistence of MPNST and plexiform neurofibroma was expected, like MPNST, skeletal dysplasia, and plexiform neurofibroma. It has been noted in a previous study that sex can be a major determining factor for neural dysfunction in NF1 disease (Diggs-Andrews et al. 2014). However, in this study we did not find any relation between the sex and clinical symptoms, especially neural defect.

In conclusion, these results offer evidence for the presence of common modifiers that affect the coexistence of symptoms, which is important for phenotypic variations in NF1. Moreover, additional studies of large populations and mechanistic studies are required to determine the molecular mechanisms of parental age effects.

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Compliance with ethical standards

Ethical statement This study was supported by the Hacettepe University Scientific Research and Development Office (Project No. H.U.BAB. 010 T02 102).

Conflict of interest The authors declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

Informed consent was obtained from all individual participants included in the study.

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