Comparison of familial Mediterranean fever and juvenile idiopathic arthritis patients according to family origin

Kenan Barut, Gizem Pamuk, Amra Adrovic, Sezgin Şahin, Aslı Kaplan, Mürüvet Güler, Özgür Kasapçopur
Istanbul University, Cerrahpaşa Medical Faculty, Department of Pediatrics, Division of Pediatric Rheumatology, Istanbul, Turkey

Cite this article as: Barut K, Pamuk G, Adrovic A, et al. Comparison of Familial Mediterranean Fever and juvenile idiopathic arthritis patients according to family origin. Turk Pediatri Ars 2018; 53: 31-6.

Abstract

Aim: Familial Mediterranean fever is an inherited condition that is more prevalent in some regions of Turkey. Juvenile idiopathic arthritis is the most common chronic arthritis of childhood. There is lack of studies on the frequency of mentioned conditions across different regions of Turkey. We aimed to compare the Familial Mediterranean fever and juvenile idiopathic arthritis patients according to their family origin.

Material and Methods: Patients with diagnosis of familial Mediterranean fever and juvenile idiopathic arthritis followed up at the Division of Pediatric Rheumatology were assessed. Data regarding the family origin of patients were noted from their medical records. Both groups were compared according to their origins.

Results: A total of 704 patients with Familial Mediterranean fever, 204 patients with juvenile idiopathic arthritis were enrolled. The main age of the patients at the study time was 12.3±4.4 years and 12.1±4.8 years, respectively. The frequency of familial Mediterranean fever was significantly higher in subjects with the origin of Black Sea and Central Anatolia regions (z score 2.69, and 3.69, respectively). Juvenile idiopathic arthritis was significantly more common in subjects from Marmara and Southeastern Anatolia regions (z score -4.11 and -2.54, respectively).

Conclusion: The familial Mediterranean fever is more common among subjects from the Black Sea and Central Anatolia regions of Turkey, especially Kastamonu, Sivas and Tokat provinces. Whereas, patients with juvenile idiopathic arthritis more commonly originate from Marmara and Southeastern Anatolia regions of Turkey.

Keywords: Family origin, familial Mediterranean fever, juvenile idiopathic arthritis, geographical regions of Turkey

Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive, inflammatory disease, which is manifested by recurrent episodes of serositis. In Turkey, the prevalence of FMF is generally known to be 1/1000 (1). However, very different prevalence rates have been reported by regions; a high prevalence was reported in Sivas from the Central Anatolia Region, and a study conducted in the Trakya region reported a prevalence of 1/17,835 (2, 3). It is known that FMF is observed more frequently in various regions of Turkey including mainly the Black Sea region. Therefore, it is very

important to question family origin for the diagnosis of FMF (1, 2). Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease of childhood with unknown etiology and different subgroups. It is predominantly manifested with peripheral arthritis (4). In different countries, its annual incidence ranges between 1/100,000 and 22/100,000, and its prevalence ranges between 7/100,000 and 150/100,000 (4, 5). There are still no sufficient data related with its prevalence in Turkey. In a previous study, the prevalence of chronic arthritis in children was reported to be 64/100,000 (6). No study related with the prevalence of JIA by provinces and regions has been conducted in Turkey. In one

Address for Correspondence: Kenan Barut E-mail: drkenanbarut@hotmail.com

Received: 26.05.2017

Accepted: 29.09.2017

©Copyright 2018 by Turkish Pediatric Association - Available online at www.turkpediatriarsivi.com

DOI: 10.5152/TurkPediatriArs.2018.5818

study, it was shown that rheumatic diseases including JIA, rheumatoid arthritis, vasculitis, and connective tissue diseases, which were compared with FMF, originated mostly from the same provinces. However, only 24 of these different rheumatic cases were reported to be JIA cases (7). We showed that chronic arthritis was also observed in patients with a diagnosis of FMF in a study we conducted in our clinic (8). In another study conducted in Turkey, it was shown that the MEFV mutation, which is the genetic mutation of FMF, was more frequent in patients with JIA compared with the carrier rate in the community (9).

No studies have compared the prevalences of FMF and JIA in Turkey by family origin. The aim of this study was to compare the provinces and regions of origin of patients with FMF and JIA who came from different regions of Turkey and who we followed up in a single center, between each other, and to show the prevalence of JIA, which is thought to be increased in patients with FMF over the same origin. In addition, it was also aimed to obtain information about the distribution of these two patient groups by regions and provinces.

Material and Methods

The files of the patients who were diagnosed as having JIA according to the Turkish FMF diagnostic criteria and the International League of Associations for Rheumatology (ILAR) diagnostic criteria in Istanbul University Medical Faculty, Division of Pediatric Rheumatology were examined in May 2017 following ethics committee approval and their family province of origin was determined (10, 11). The follow-up files of the children who were included in the study were created after January 1st, 2002, and all were below the age of 18 years. Information related with the family origin was obtained from the follow-up files in all patients and confirmation was made through face-to-face interviews or by phone calls. The sex and age of all subjects were recorded. A separate map was established for each patient group by averaging both maternal and paternal origin numbers on a map of provinces of Turkey in order to show the intensity of the cases by province. The provinces were divided by their relevant geographic regions and the frequencies of both groups by regions were demonstrated with graphics and tables. Informed consent was obtained from the parents of the patients in both groups and from the patients themselves if they were aged above 12 years. Ethics committee approval was obtained for the study (Istanbul University Cerrah-

paşa Medical Faculty Ethics Committee. Date and number: 03/05/2017-166 591)

Statistical Analysis

The patient groups were divided into percentiles according to their province of origin, and the regions that these provinces were linked to were determined and classified in themselves. The z test was used to statistically compare the differences between the rates of maternal and paternal origins in both the FMF and JIA groups. The z test that we used in our study is a statistical test for evaluating whether there is any difference between the unit rates related to any characteristics in two independent groups (the formula used for the z test is shown below). In this comparison, the regions for which a significance level of 0.05 was reached were considered statistically significant ($|z| > 1.96$) and the regions for which a significance level of 0.01 was reached were considered extremely significant ($|z| > 2.58$).

Results

In this study, 704 patients with FMF were evaluated; 344 (48.9%) were female and 360 (51.1%) were male. The mean age of the patients at the time of the study was 12.3 ± 4.4 years. When the maternal and paternal origins of the patients with FMF examined, the provinces in which FMF was found most commonly included Sivas [mother n=86 (12.1%), father n=82 (11.6%)], Kastamonu [mother n=59 (8.3%), father n=64 (9%)], Tokat [mother n=56 (7.9%), father n=54 (7.6%)], Sinop [mother n=37 (5.2%), father n=40 (5.6%)], Ordu [mother n=38 (5.4%), father n=32 (4.5%)], and Samsun [mother n=28 (3.9%), father n=27 (3.8%)]. The frequencies of family origins among the patients with FMF in all provinces are shown in Figure 1. Differentiation by geographic regions of Turkey could be assessed in 696 mothers and 698 fathers. When the provinces were assessed by the relevant geographic region, the highest number of patients with FMF originated from the Black Sea region. The frequencies by geographic regions according to maternal and paternal origin are shown in Figure 2 and Figure 3, respectively.

Two hundred four patients comprised the group with JIA; 121 (59.3%) were female and 83 (40.7%) were male. The mean age of the patients with JIA was 12.1 ± 4.8 years. The most common family province of origin among patients with JIA included Ordu [mother n=10 (4.9%), father n=13 (5.9%)], Kastamonu [mother n=9 (4.4%), father n=13 (6.4%)], Sivas [mother n=11 (5.4%),

Figure 1. Distribution of the maternal origins of patients with familial Mediterranean fever and juvenile idiopathic arthritis by geographic regions

Figure 2. Distribution of the paternal origins of patients with familial Mediterranean fever and juvenile idiopathic arthritis by geographic regions

father n=6 (2.9%), Trabzon [mother n=10 (4.9%), father n=7 (3.4%)], Samsun [mother n=7 (3.4%), father n=8 (3.9%)], and Istanbul [mother n=9 (4.4%), father n=6 (2.9%)]. The frequency of family origins of the patients with JIA in all provinces are shown in Figure 4. Differentiation by geographic regions of Turkey could be evaluated in 198 mothers and 194 fathers. The highest number of patients with JIA was observed in families originating from the Black Sea region, but the difference found for JIA in the Black Sea region in comparison with FMF was not statistically significant. The rates by the other regions are shown according to mothers and fathers in Figure 2 and Figure 3, respectively. In the comparison of the regions between themselves, it was found that patients who were being followed up with a diagnosis of FMF mostly originated from the Central Anatolia region and Black Sea region, and the pa-

tients with JIA mostly originated from the Southeastern Anatolia region and Marmara region. This comparison, which was performed by considering maternal and paternal origins, showed an extremely statistically significant difference (Table 1). The differences in the other regions were not statistically significant.

Discussion

In patients with FMF, family origin is important for the diagnosis of the disease, though it is not included in the diagnostic criteria (1, 12). The disease is observed frequently in Jewish, Arabic, Armenian, and Turkish communities. In Turkey, cases of FMF are observed more frequently in the provinces of the Central Anatolia region including Ankara, Tokat, Sivas, and Kayseri, in the provinces of the Black Sea including Kastamonu, Sinop,

Figure 3. Intensity map according to the family origins of province of the patients with familial Mediterranean fever

Figure 4. Intensity map according to the family origins of province of patients with juvenile idiopathic arthritis

Gümüşhane, Giresun, and Bayburt, and in provinces of the Eastern Anatolia region including Erzincan, Erzurum, Malatya, Kars, and Ağrı. The disease intensifies mostly in the internal regions of the Black Sea region facing the Central Anatolia and Eastern Anatolia regions (13). In our study, it was found that the provinces in which FMF was observed with a high rate overlapped with these provinces.

Although the prevalence of FMF by regions in Turkey is known, there are no data showing the origins of geographic region of patients with JIA. In a study conducted in 1997 from Cerrahpaşa Medical Faculty, 121 patients with FMF and 154 patients with different rheumatic diseases were investigated in terms of province

of origin and it was shown that family origin intensified in the Central Anatolia region, especially in Sivas in both patient groups (7). However, it was difficult to state that JIA was also observed frequently in the regions where FMF was observed frequently because the study only included 24 patients with JIA.

In our study, it was found that patients with FMF and JIA mostly originated from provinces including Sivas, Ordu, Tokat, Kastamonu, and Samsun. According to the Turkish Statistical Institute (TÜİK) 2015 data, it was shown that the most common origins of people living in Istanbul included abroad, Sivas, Ordu, Tokat, and Samsun (14). In our study, it was observed that the origins of the patient groups were mostly shaped ac-

Table 1. Comparison of the family origins of the patients with familial Mediteranean fever and juvenile idiopathic arthritis between each other by geographical regions

	Maternal origins (n, %)		Maternal origins FMF and JIA (z statistics)	Paternal origins (n, %)		Paternal origins FMF and JIA (z statistics)
	FMF	JIA		FMF	JIA	
Marmara Region	27 (3.9)	29 (14.6)	-4.11 ^b	27 (3.9)	25 (12.8)	-3.59 ^b
Central Anatolia Region	161 (23.1)	25 (12.6)	3.69 ^b	152 (21.7)	22 (11.3)	3.78 ^b
Eastern Anatolia Region	116 (16.6)	44 (22.2)	-1.70	147 (21.1)	41 (21.1)	-0.02
Southeastern Anatolia Region	30 (4.3)	20 (10.1)	-2.54 ^a	25 (3.6)	23 (11.8)	-3.41 ^b
Black Sea Region	341 (48.9)	76 (38.4)	2.69 ^b	330 (47.3)	79 (40.7)	1.64
Aegean Region	6 (0.9)	3 (1.5)	-0.70	5 (0.7)	3 (1.6)	-0.88
Mediterranean region	15 (2.2)	1 (0.5)	2.21 ^a	12 (1.7)	1 (0.5)	1.69

FMF: Familial Mediterranean fever; JIA: Juvenile idiopathic arthritis; a: regions where statistical difference was significant at a significance level of 0.05 ($|z| > 1.96$); b: regions where statistical difference was significant at a significance level of 0.01 ($|z| > 2.58$)

cording to provinces that admitted immigrants. Istanbul was among the most common origins of province in the JIA group, but not in the FMF group.

Owing to social and economic reasons, the direction of migration experienced in Turkey is generally from the Black Sea, Eastern Anatolia, and Southeastern Anatolia regions towards the industrialized provinces in the Western regions with high income per capita (15). The regions with the highest level of socioeconomic development include the Marmara and Aegean regions (15, 16). In our study, Black Sea region origin was found with the highest frequency in both groups; the highest rate was found in the FMF group and an extremely statistically significant difference was found. The regions of Turkey with the highest levels of emigration include Eastern Anatolia, Southeastern Anatolia, the Northern part of the Central Anatolia, and the Black Sea region (16). When we evaluated the origins of geographic region on the map in our study, we found that cases of FMF mostly intensified in the northern part of the Central Anatolia and the Black Sea region and origins of patients with JIA showed a distribution of Eastern Anatolia, Southeastern Anatolia, and the Black sea region, as was observed in the migration map in the literature (16).

According to the Turkish Statistical Institute 2015 data, the provinces that admitted immigrants with the highest rate included Istanbul, Ankara, Izmir, Bursa, and Antalya (14). Among these provinces, excluding Istanbul, these provinces generally admitted immigrants from nearby provinces, whereas Istanbul mostly accepted immigrants from the Black Sea region, as mentioned

above. The finding that few cases originated from regions where other large industrialized provinces were found in our study could be explained with migration from these provinces towards nearby industrialized provinces. Considering that immigration occurs because of socioeconomic reasons, it was observed that the provinces from which patients with JIA originated were compatible with the information that immigration occurs from regions with low socioeconomic levels towards more developed regions. The Marmara region is known as the region that accepts immigrants at the highest rate in Turkey (15, 16). When the patients with FMF and those with JIA were compared, it was found that JIA was more common in patients originating from the Marmara region, and this was extremely statistically significant. Similarly, JIA was found more commonly in the Southeastern Anatolia region compared with FMF and this difference was extremely statistically significant.

It is known that the Black Sea region and Central Anatolia region are among the regions where FMF is observed most intensively (1, 13). In our study, it was shown that family origins among the patients with FMF arose from the Black Sea and Central Anatolia regions with a much higher rate compared with those with JIA, and such a high level of difference was not seen in the other regions. This indicates the regions in which FMF can actually be found intensively. In the Southeastern Anatolia region, JIA was observed with a much higher rate compared with FMF. It is known that the Southeastern Anatolia region is an underdeveloped region according to the socioeconomic development

index (16). In studies conducted in this region, FMF has been shown to be frequent (17), but there are no studies related with JIA.

The limitations of our study are as follows: the JIA group included a lower number of subjects. If the number of subjects were higher, much stronger statistical results could be obtained. If the socioeconomic level could be determined with a questionnaire evaluation, a relationship between the socioeconomic level and FMF and JIA could be demonstrated. In addition, our results could not be supported by prevalence studies because there are no prevalence studies related with JIA.

In conclusion, it was shown that FMF occurred more frequently in families originating from the Black Sea and Central Anatolia regions. Sivas, Kastamonu, and Tokat were the provinces where the highest level of intensity was observed. Juvenile idiopathic arthritis was found with a higher rate in families originating from the Marmara and Southeastern Anatolia Regions. As with FMF, prevalence studies related with JIA need to be conducted across Turkey.

Ethics Committee Approval: Ethics committee approval was received for this study from Istanbul University Cerrahpasa Medical Faculty Ethic Committee (03/05/2017-166 591).

Informed Consent: Written informed consent was obtained from the parents.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - K.B., Ö.K.; Design - K.B., G.P., S.Ş.; Supervision - Ö.K., A.A., S.Ş.; Funding - K.B., G.P.; Materials - M.G., A.K., G.P.; Data Collection and/or Processing - K.B., A.K., M.G.; Analysis and/or Interpretation - K.B., Ö.K., A.A.; Literature Review - K.B., A.A., A.K., M.G.; Writing - K.B., S.Ş.; Critical Review - Ö.K., A.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare that this study has received no financial support.

References

1. Tunca M, Akar S, Onen F, et al. Familial Mediterranean fever (FMF) in Turkey: results of a nationwide multi-center study. *Medicine* 2005; 84: 1-11. [\[CrossRef\]](#)
2. Onen F, Sumer H, Turkay S, Akyurek O, Tunca M, Ozdogan H. Increased frequency of familial Mediterranean fever in Central Anatolia, Turkey. *Clin Exp Rheumatol* 2004; 22: 31-3.
3. Cakir N, Pamuk ON, Dervis E, et al. The prevalences of some rheumatic diseases in western Turkey: Havsa study. *Rheumatol Int* 2012; 32: 895-908. [\[CrossRef\]](#)
4. Barut K, Adrovic A, Şahin S, Kasapçopur Ö. Juvenile idiopathic arthritis. *Balkan Med J* 2017; 34: 90-101. [\[CrossRef\]](#)
5. Prakken B, Albani S, Martini A. Juvenile idiopathic arthritis. *Lancet* 2011; 377: 2138-49. [\[CrossRef\]](#)
6. Ozen S, Karaaslan Y, Ozdemir O, et al. Prevalence of juvenile chronic arthritis and familial Mediterranean fever in Turkey: a field study. *J Rheumatol* 1998; 25: 2445-9.
7. Yazıcı H, Ozdogan H. Familial Mediterranean fever in Turkey. *Familial Mediterranean fever 1 international FMF conference proceeding Book*. 1997; 1: 66-71.
8. Barut K, Sahin S, Adrovic A. et al. Familial Mediterranean fever in childhood: a single center experience. *Rheumatol Int* 2018; 38: 67-74 [\[CrossRef\]](#)
9. Comak E, Dogan CS, Akman S, Koyun M, Gokceoglu AU, Keser I. MEFV gene mutations in Turkish children with juvenile idiopathic arthritis. *Eur J Pediatr* 2013; 172: 1061-7. [\[CrossRef\]](#)
10. Yalcinkaya F, Ozen S, Ozcakar ZB, et al. A new set of criteria for the diagnosis of familial Mediterranean fever in childhood. *Rheumatology* 2009; 48: 395-8. [\[CrossRef\]](#)
11. Petty RE, Southwood TR, Manners P, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol* 2004; 31: 390-2.
12. Yalcinkaya F, Ozen S, Ozcakar ZB, et al. A new set of criteria for the diagnosis of familial Mediterranean fever in childhood. *Rheumatology* 2009; 48: 395-8. [\[CrossRef\]](#)
13. Kasapçopur Ö, Arısoy N. Ailesel Akdeniz ateşi ve diğer otoenflamatuvar hastalıklar. *Turk Pediatri Ars* 2006; 41: 9-17.
14. Türkiye istatistik kurumu. Doğum yeri istatistikleri 2015; 24562.
15. Bülbül S, Köse A. Türkiye’de bölgelerarası iç göç hareketlerinin çok boyutlu ölçekleme yöntemi ile incelenmesi. *İstanbul Üniversitesi İşletme Fakültesi Dergisi*. 2010; 39: 75-94.
16. Yakar M. Türkiye’de iller arası net göçlerle sosyo-ekonomik gelişmişlik arasındaki ilişkinin coğrafi ağırlıklı regresyon ile analizi. *Ege Coğrafya Dergisi* 2013; 22: 27-43.
17. Ece A, Cakmak E, Uluca U, et al. The MEFV mutations and their clinical correlations in children with familial Mediterranean fever in southeast Turkey. *Rheumatol Int* 2014; 34: 207-12. [\[CrossRef\]](#)