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Air pollution, a possible risk factor for multiple sclerosis

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Objective: Studies focusing attention on the effects of environmental pollution on the etiology of multiple sclerosis (MS) are on the increase. The aim of this study was to determine MS prevalence in a city home to an iron and steel factory which causes air pollution.

Methods: The study was designed as a cross-sectional, population-based, descriptive epidemiologic study. Ereğli city, which has an iron and steel factory and proven air pollution, was screened. Additionally, Devrek city, which is a rural and clean city, located 40 km away from Ereğli was assigned and results were compared. A validated questionnaire was used for screening. McDonald 2010 criteria were used to diagnose cases.

Results: 32 261 people were screened in Ereğli, and 21 963 people were screened in Devrek. In total, 41 patients were diagnosed with clinical definite MS. Crude prevalence was found to be 96.1/100 000 in Ereğli and 45.5/100 000 in Devrek. The mean age of patients was 39.8, and the female/male ratio was 1.9.

Conclusion: The results of this study indicate a more than double MS prevalence rate in the area home to an iron and steel factory when compared to the rural city. This supports the hypothesis that air pollution may be a possible etiological factor in MS.

KEYWORDS

air pollution, community-based study, epidemiology, multiple sclerosis, Turkey

1 | INTRODUCTION

Multiple Sclerosis (MS) is a chronic disease of the central nervous system (CNS) characterized by inflammation and neurodegeneration. MS is the leading cause of serious neural disability in young adults. Although various studies of the environmental risk factors suggest a link between exposure to environmental factors and MS, there is still much that remains unknown. Possible environmental factors in MS include infection agents, low exposure to sunlight, vitamin D deficiency, exposure to chemical substances, air pollution, smoking, and socioeconomic factors.[1,2] Evidence suggesting a link between ambient air pollution and MS is limited. Oikenen et al[3] recorded a direct relationship between the frequency of MS relapses and airborne particulate matter. A study from Iran observed that greater exposure to pollution was more common in cases than in controls.[4]

Studies carried out on MS epidemiology in Turkey indicate that the prevalence of MS is changing in variety according to cities characteristics.[5-7] An epidemiological study conducted in Karabük city, which has proven air pollution and is home to an iron and steel factory, highlighted almost a twofold prevalence when compared to other cities.[8] On the other hand, another study showed the lowest ever national MS prevalence recorded, which was in Artvin city, the cleanest city in Turkey.[5]

In light of these studies, we aimed to assess the prevalence of Ereğli city which also has an iron and steel factory as well as proven air pollution and to compare the results with a control population in neighboring Devrek city, a city without any air pollution.

2 | MATERIAL AND METHODS

This study was designed as a cross-sectional descriptive epidemiological door-to-door field study. The study was carried out over a 5-month period between May 2018 and October 2018.

2.1 | Ethical approval

The study was approved by the Local Ethics Committee at Dr Lütfi Kırdar Kartal Training and Research Hospital (Approval No: 2017/514/106/1).

2.2 | Characteristics of screening areas

Karadeniz Ereğli is located in the north east Black Sea region connected to Zonguldak city. It is located at latitude 41.17°N and longitude 31.24°E. Its surface area is 782 km^2, and it is located at 5 m above sea level. It has a 120 km coast line along the Karadeniz Ereğli borders. 65% of the city is covered in trees. The climate is warm and wet. The average annual temperature is 13.5°C, and average annual rainfall is 1048 mm. The population consists of homogeneous Turkish people. According to the 2016 census, the population is 115 987.[9] The population originates from the Çepni branch of the Oğuz tribe. There are two state hospitals which have a capacity of 700 beds. There are also two private hospitals and clinics located in the city center. There are approximately 100 medical doctors. It is easy to access a neurologist and MRI devices. There are many rich coal mines and an iron and steel factory which is located in the city center which has been in operation since 1961. There are an additional 15 industrial establishments. The main sources of income are mining and industry as well as forestry, fishing, and farming.[10] Air pollution records from 2012 to 2017 are shown in Table 1. According to this figure, air pollution exists in Ereğli.[11]

Devrek is a small city neighboring Ereğli in the Zonguldak province. The distance between Ereğli and Devrek is 40 km. It is located at latitude 41.22°N and longitude 31.95°E. It is 100 m above sea level, and it is 32 km from the sea. The geographical and climate conditions are almost identical to those of Ereğli. The main sources of income include agriculture, forestry, and carpentry. Its racial, economic, and cultural characteristics are almost identical to Ereğli's. According to the 2016 census, the population is 24 215.[9] Unlike Ereğli, Devrek is not home to a factory; therefore, it has a low number of laborers. There is one state hospital which has a capacity of 136 beds. There are also two private hospitals and clinics located in the city center. There are approximately 50 medical doctors. It is easy to access a neurologist and MRI devices.[12] There are no factories which can cause air pollution. Areas which have been measured and have proven air pollution are provided with a permanent air pollution observational station. According to the mobile national air monitoring network stations, Devrek has not been reported to have air pollution (pollutant levels: PM_{10} < 20 μg/m3, SO_2 < 20 μg/m3, NO_2 < 40 μg/m3). Thus, a permanent station has not been established in Devrek unlike Ereğli.[11]

2.3 | Study area and participants

The Ereğli study area was determined based on the location of the iron and steel factory. Firstly, the iron and steel factory was marked as the center of the study area. A 2 km radius chamber was drawn with the factory at its center. The Ereğli study area is shown in Figure S1. The population living inside the 4 km study area is approximately 35 000 people. All households inside this semicircular area were targeted for screening.

The Devrek study area consisted of the entire district. All households in the district and the entire population of Devrek (24 215 people) were targeted for the screening. The locations of Devrek and Ereğli cities on the Black Sea and Turkey maps are shown in Figures 1 and 2.

2.4 | Screening forms

We used the validated screening forms that we had used in our prevalence study conducted in Maltepe, Istanbul in 2002.[13] The questionnaires consisted of 26 questions in two sections. The first section assessed knowledge about MS and the second addressed MS symptoms. The questions enquired about the presence of present and past symptoms, motor and sensory dysfunction, walking

TABLE 1 Air pollutant values of Ereğli and Devrek by year and WHO threshold values

Air pollutants	2012	2013	2014	2015	2016	2017	WHO
Ereğli							
PM_{10} (μg/m3)	497	293	218	350	309	197	20
SO_2 (μg/m3)	225	139	93	221	104	86	20
NO_2 (μg/m3)	156	1108	194	247	243	119	40
Devrek							
PM_{10} (μg/m3)	<20	<20	<20	<20	<20	<20	20
SO_2 (μg/m3)	<20	<20	<20	<20	<20	<20	20
NO_2 (μg/m3)	<40	<40	<40	<40	<40	<40	40

FIGURE 1 Locations of Devrek and Ereğli Cities on Turkey Map

FIGURE 2 Locations of Devrek and Ereğli Cities on Turkey Map

ability, sphincter control, sleep, balance disturbances, ataxia, depression, increased fatigability, and memory disturbances.

2.5 | Study procedure

In order to increase public participation, we worked together with the Ereğli and Devrek Public Health Centers. All participants were briefed on the study at the local health center with the aid of a brochure. Starting from 15 days prior to the start of the study, the local council made regular announcements regarding the study.

Teams were assembled 1 week prior to the start of the study. Five teams consisting of five persons (a neurologist, a nurse, and three medical students per team) were grouped together in order to obtain reliable and precise data with the correct provisional diagnosis. The teams were informed about the screening and the symptoms of MS over a 5-day period. The location of the screening was divided into five areas and designated to each team.

All houses to be visited were determined in advance, and in cases where no one was home, the same house was revisited later, up to three times if necessary. The teams conducted their visits between 09:30 a.m. and 4:30 PM both on weekdays and weekends. If a patient had communication difficulties, a person responsible for their care was interviewed in their place.

The field study was divided into two sections. The first section asked questions directly to the participants, and answers were written down. Participants who answered yes to at least one question about MS symptoms were examined by the team neurologist on site.

In the second section, patients suspected of having MS were called back and re-examined by the first author of the study.

2.6 | Case ascertainment

Once examination was completed, all previous medical records including MRI findings and immunologic examinations were reviewed

and recorded. McDonald 2010 criteria were used in the diagnosis of MS.[14] Neurological disease severity was assessed using the Kurtzke's Expanded Disability State Score (EDSS).[15]

2.7 | Statistical analyses

Statistical analyses were performed using PASW Statistics 18.0 software. Frequency distribution, percentage, mean, and standard deviation were calculated where appropriate. Minitab statistical software (version 16, SPSS Inc) was used for calculating the Poisson confidence intervals and comparing prevalence rates.

3 | RESULTS

3.1 | Ereğli's findings

In total, 33 794 people were reached in Ereğli, 1533 refused to take part in the study. 32 261 persons were screened. Participation was 95.4%. Out of this number, 43 people were suspected of having MS and were called back to be re-examined and their medical records were also reviewed. 31 persons were diagnosed with clinical definitive multiple sclerosis (CDMS). Of these, 25 had RRMS. 5 had SPMS, 1 had PPMS. 19 were female, 12 were male. The mean duration of disease was 12 ± 9 years. The mean EDSS was 3.1 ± 2.1. Family history was present in three patients. Out of the twelve remaining persons, one was diagnosed with spinocerebellar ataxia, one with Duchenne muscular dystrophy, four with stroke, two with diabetic polyneuropathy, two with lumbar disk herniation, and one with ALS. A 17-year-old girl had suffered an optic neuritis attack. Her neurological examination was normal. Laboratory findings including cranial and spinal MRI and CSF findings were normal. She was diagnosed with clinical isolated syndrome.

The crude MS prevalence of Ereğli was found to be 96.1/100 000. After age standardization to the Turkish population (2018 census), it was found to be 97.4/100 000.

3.2 | Devrek's findings

24 016 people were reached. 2053 refused to take part in the study. In total, 21 963 persons were screened in Devrek. The participation rate was 91.4%. In total, 17 persons were suspected of having MS and were called back for a second examination. 10 persons were diagnosed with CDMS. Of these, 8 had RRMS and two had SPMS. 8 were female, and 2 were male. The mean duration of disease was 13.7 ± 8.5 years. The mean EDSS was 4.4 ± 2.8. One patient had family history.

Out of the remaining seven persons, 2 were diagnosed with stroke, 2 with diabetic polyneuropathy, 1 with Parkinson's disease, 1 with a brain tumor, and 1 with sequelae of meningitis.

TABLE 2 Demographic characteristics, initial symptoms, and laboratory findings of the patients

Characteristics	
Number of cases	41
Female/male	1.9
Age, y, mean ± SD	39.8 ± 11.7
Duration of disease onset, y, mean ± SD	12.4 ± 8.9
EDSS, mean ± SD	3.8 ± 2.3
DMDs treatment	34
Total attacks, mean ± SD	6.2 ± 3.5
Initial symptoms	
Pyramidal, n (%)	9 (21.9)
Cerebellar, n (%)	6 (14.6)
Brainstem, n (%)	7 (17.1)
Sensorial, n (%)	8 (19.5)
Visual, n (%)	11 (26.8)
Laboratory findings positivity	
Brain MRI, n	41/41
Spinal MRI, n	23/34
CSF OCB, n	28/33
Aquaporin-4, n	0/19

Abbreviations: CSF, cerebrospinal fluid; DMDs, disease-modifying drugs; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; OCB, oligoclonal band; SD, standard deviation.

The crude prevalence was found to be 45.5/100 000. After age standardization to the Turkish population (2018 census), it was found to be 47.2/100 000.

3.3 | Summation

The results of MS patients from both cities are summarized in the tables respectively. Demographic and clinical characteristics, the initial symptoms, and laboratory findings of patients are shown in Table 2. Age-standardized prevalence is shown in Table 3.

4 | DISCUSSION

The results of this study recorded a significantly high MS prevalence of 96.1/100 000 in Ereğli which is home to an iron and steel factory, and a much lower MS prevalence of 45.5/100 000 in Devrek which is a neighboring city of Ereğli.

When we compare the two areas, their geographical, racial, social, and cultural characteristics are very similar. A possible explanation for such a high prevalence may be due to environmental factors. A previous study carried out in Karabük in Turkey, which is also home to an iron and steel factory and has proven air pollution, supports this claim. The prevalence was found to be 95.9/100 000.[8]

TABLE 3 Age-standardized prevalence of Ereğli and Devrek

	Ereğli			Devrek		
Age group	Case number	Population	Age-specific prevalence (/100.000)	Case number	Population	Age-specific prevalence (/100.000)
Study data						
0-9	0	4399	0	0	2041	0
10-19	0	4757	0	1	2437	41
20-29	11	4206	261.5	0	2363	0
30-39	9	5323	169.1	3	2973	100.1
40-49	7	4942	141.6	4	2835	141.1
50-59	2	3983	50.2	2	3590	55.8
60-69	2	2838	70.5	0	3229	0
70-79	0	1247	0	0	1723	0
80+	0	566	0	0	772	0
Total	31	32 261	96.1	10	21 963	45.5
	Ereğli			Devrek		
Age group	Population (Turkey)	Estimated case numbers	Age-specific prevalence (/100 000)	Population (Turkey)	Estimated case numbers	Age-specific prevalence (/100 000)
Estimated case numbers for 2018 Turkey population						
0-9	12 822 618	0	0	12 822 618	0	0
10-19	12 737 457	0	0	12 737 457	5222	41
20-29	12 688 052	33 179	261.5	12 688 052	0	0
30-39	12 857 620	21 742	169.1	12 857 620	12 870	100.1
40-49	10 795 973	15 287	141.6	10 795 973	15 233	141.1
50-59	8 642 182	4338	50.2	8 642 182	4822	55.8
60-69	5 883 142	4148	70.5	5 883 142	0	0
70-79	2 986 452	0	0	2 986 452	0	0
80+	1 397 029	0	0	1 397 029	0	0
Total	80 810 525	78 694	97.4	80 810 525	38 147	47.2

TABLE 4 Air pollutants levels of Istanbul

Air pollutants	2012	2013	2014	2015	2016	2017	WHO
PM_{10} (µg/m3)	186	281	177	419	625	82	20
SO_2 (µg/m3)	36	17	8	17	11	15	20

Abbreviations: WHO, World Health Organisation threshold values.

TABLE 5 Results of studies from different Turkish cities

Areas	Years	Screened population (n)	Crude prevalence (/100 000)
İstanbul[13]	2002	32 531	101.4
Geyve[5]	2006	17 016	41
Kandıra[5]	2006	8171	61
Erbaa[5]	2006	28 177	53
Karabük[8]	2014	28 127	95.9
Akçakoca[8]	2014	12 992	46.1

Another study from Maltepe, İstanbul, conducted in 2002 recorded the highest national prevalence (101.4/100 000) to date.[13] Istanbul is also a megacity, home to more than 15 000 000 people with a high urbanization rate, high levels of air pollution, traffic, artificial lighting, and noise pollution. The PM_{10} levels are 4-30 times above the WHO threshold.[11] Pollutant levels are shown in Table 4. The lowest national MS prevalence 18.8/100 000 was found in Artvin which is the cleanest city in Turkey according to the national air observation center.[11] Results of the studies on MS epidemiology in Turkey are summarized in Table 5.

When we analyze the epidemiologic studies from Turkey, it can be seen that the highest prevalence rates of MS are from the most air-polluted cities.

The relationship between air pollution and MS has been suggested in a number of studies. A study recorded a significant link between the clustering of MS patients and concentration patterns of PM_{10}, SO_2, NO_x in Tehran.[4] USA, French, and Italian studies have suggested a relationship between exposure to air pollution and the occurrence of MS relapses and hospitalization.[16-18] Dehghani et al[19] showed that the prevalence in various Iranian provinces was directly linked to its urbanization and that provinces with a higher urbanization rate had a higher MS prevalence.

Basically, air pollution can affect the brain in two pathways. Firstly, by direct pathways where pollutants reach the brain injure parenchyma. Secondly, air pollution-induced effects in the periphery impact the brain indirectly. It has been established that pro-inflammatory signals, which originate in tissues and organs including the lungs, liver, circulating immune cells, and the cardiovascular systems which are peripheral to CNS, are caused by urban air pollution and this often results in circulation cytokine response which can then activate microglia transferring inflammation to the brain.[20-24]

In addition, in vitro studies with human airway epithelial cells show that exposure to PM_{10} particles activates pro-inflammatory genes in a process mediated by free radical/oxidative stress mechanisms.[25-27]

4.1 | Limitations of the study

The major limitation of this study is its small study population and case number. Another limitation of the study is that we did not investigate other cofounder factors such as Vit D level, infections agents, vaccinations, smoking, and exposure to sunlight. Additionally, applying McDonald criteria may be inadequate in differentiating between MS mimics. Another limitation is that we did not compare the degree of air pollution with the onset of MS. Information is lacking about the duration of the residency of affected individuals in the high-risk area.

4.2 | Strengths of the study

A strength of the study is that it was carried out by a neurologist and a local nurse on site. All participants suspected of having MS were examined on site by the neurologist. All their medical records were reviewed by the neurologist, and their results were recorded. At the end of the study, all patients that were called back were re-examined by an experienced neurologist (UTB).

5 | CONCLUSION

The results of this study suggest that air pollution may be an etiological factor in MS. More case-control studies investigating environmental effects on MS are needed in order to shed more light on this area.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

AUTHOR CONTRIBUTIONS

All authors contributed to study design, writing the paper, and its revision. CB and MT were responsible for data collection and analysis.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available on request from the corresponding author CB.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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