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Original Article

Effect of Air Pollutant Markers on Multiple Sclerosis Relapses

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Abstract

Background: Multiple Sclerosis (MS) is one of the autoimmune diseases with an unknown cause. The aim of this study was to explore the link between air quality and MS relapses in patients who suffer from MS.

Methods: This time-series study was conducted on patients registered at the Iranian Multiple Sclerosis Society in 2011-2012. They were randomly selected from patients lived in Tehran in the last five years, and had at least one relapse in the last three years. The link between monthly mean air pollutant levels and the relapses of MS in the participants was studied.

Results: Among the registered 160 participants, at least 150 had one attack during 2009 and 2012. Most air pollutants such as NO2, NO and CO are in high levels in the rainy season. Others like Pm10 and Nox are in high levels in the dry season. The correlation between NO2 levels of all markers of air quality and MS relapses (P=0.03, r=0.27) is weak. Best ARIMA model (p,d,q; 1,0,1) was determined between number of monthly relapses and living place, although this model was not significant (P=0.3) (AR; P=0.000, MA;P=0.4).

Conclusions: Air pollutants might be regarded as a risk factor for MS relapse.

Keywords: Multiple sclerosis, Air pollutants, Time series, Iran

Introduction

Outdoor air pollutants are a combination of dangerous gases (e.g. ozone), organic compositions and particulate matters (PMs). Current studies have illustrated that air pollution can aggravate neurological disorders (1, 2). Air pollutants increased Cyclocygenase-2 and repositioned 42-Aminoacid which was the cause of neurological disorders in some cases. The results demonstrated that air pollutants are the direct cause of developing brain inflammation, neurotic plaques and neuro-fibrillary tangles, and that these symptoms are hallmarks of Alzheimer disease (2). The middle portion of the brain is more sensitive to air pollutants and neuro-inflammatory agents than other parts of the central nervous system. Neuro-inflammatory agents are recognized as pre-clinical markers for neurodegenerative diseases such as Parkinson and Alzheimer disease (3). Some evidences revealed that particulate matter will cause damage to CNS through oxidative stress pathway; and it can have a neurotoxic effect on the nervous system (4). In addition to neurodegenerative dis-

eases, long term exposure to high level of NO_2 and CO the two main air pollution components, may cause stroke in the nerves system (5, 6). Some studies demonstrated a link between air pollution and the mortality rate due to ischemic and hemorrhagic stroke. It was also determined that people who have a short term exposure to air pollution are at high risk of intra-cerebral hemorrhage and ischemia (6).

Multiple Sclerosis (MS) is a chronic condition of demyelization of nerves. It is mostly seen in young people (7). It is one of the neurological disorders which is influenced by environmental factors such as air pollution and PM concentrations (8).

Just one study, which was in Finland, could reveal that PMs are associated with the recurrence of MS (8), and since little is known about the effects of the levels of air pollutants on MS relapse rate, hence the goal of this study was to observe air pollution markers on monthly basis and examine its relationship with MS aggravation.

Method and Materials

In this ecological time-series study patients were selected from MS Society of Iran. Out of the 8146 patients in this society, almost one thousands of them were living in Tehran, of which 174 patients were chosen randomly for this research which was conducted from December 2011 to July 2012. The proof for the existence of MS in these patients was based on the diagnosis made by a neurologist and the Poser Criteria (9). From 174 participants included in this study, 160 filled the check list over telephone, directly.

The patients should have lived in one of the areas of Tehran Municipality at least for 5 years, having been affected for more than 3 years, and not being part of the Primary Progressive .

"Relapse" was defined as abnormal changes in the patient's physical status in a way that after diagnosis by the neurologist, the patient receives corticosteroids therapy or is hospitalized. The patient's place of education or occupation was also taken into consideration.

Air pollutants

Sulfur dioxide (SO2), ozone (O3), nitrogen dioxide (NO2), carbon monoxide (CO), and particulate matter less than 10μ (PM10) were taken into consideration as pollutants and the Pollutant Standards Index (PSI) was used as an indicator of the level of air pollution. There are 25 air pollution control stations in Tehran, and these data were collected from five main air quality control stations located in south, central, east, west and north Tehran. The monthly mean of these recorded data was used for statistical analysis.

Influenza viral load

Since April 2009, the data about patients with influenza was collected through a surveillance system for influenza implemented by Ministry of Health and Medical Education (MOHME) of Iran from more than 17,000 centers collecting the information of influenza affect. The data used in this study is from patients suffering with flu, and the monthly flu data was taken into consideration.

Clinical presentation of influenza included the following symptoms: high level fever (>38°C) or at least two of the following respiratory symptoms such as: cough, nasal obstruction /rhinorrhea, and fever/feverishness. Disease was confirmed by reverse transcriptase PCR (RT-PCR) for Influenza. Susceptible influenza patients were taken into account (10). Medical Ethics: The patient's letter of consent was obtained from all individuals participating in this study. This study was approved by the Medical Ethics Committee of Tehran University.

Statistical analysis

The distributions of these quantitative data were examined by one sample K-S test analysis. The relationship between air pollutants and MS aggravation was measured by using Spearman`s correlation. The linear relationship between these markers and relapse rate was examined by the forward method linear regression.

The time lag of MS relapses was unknown; 1, 12, and 36 month(s) time lag for time series analysis was chosen. Based on the examination of different ARIMA models, the best model was selected and

reported. For time series analysis the ARIMA model was used. This analysis is preferable to regression, because the data used in this study were not independent observations and autocorrelation would lead to biased results in linear regression. The components of ARIMA model, e.g. autoregressive component, were marked in plots, and the final model was expressed as ARIMA (p, d, q). Final ARIMA (1, 0, 1) model was selected after examining other models.

Results

Participant's characteristics

One hundred and fifteen patients from the one hundred and sixty participants had one minimal attack since 2009-2012. Twenty six males and eighty nine females participated. Other demographic details are provided in Table 1. Most participants were young (12-85 years) (Mean ± SD; 34.4 ± 9.5). Most of the patients were married and had moderate education (Bachelor's degree). Relapsing-remitting type of MS was higher (84, 73%). The median duration of MS was 5 years (2-30, Table 1).

Air pollution markers characteristics

Most of the air pollutants such as NO2, NO and CO are in high level in the rainy season. Other air pollutants like Pm10 and Nox are in high level in the dry season (Table 2).

Air pollutants markers and MS relapses

The mean concentration of the air pollutants markers (PM10, Co, NO2, NO, SO2 and O3) are given in Table3. A poor correlation was found between NO2 level from all markers of the air quality and MS relapses (*P*=0.03, r=0.27). NO2 and NO levels varied conversely. Although this variation was not significant (*P*=0.1, r= -0.19) in the last year, MS relapses were not confirming with normal distribution (*P*=0.05).

Table 1: Demographic characteristics of all participants

Demographic details	Number (%)
Gender	
Male	26(22.6)
Education	
Under diploma	6(5.2)
Undergraduate	41(35.7)
Graduated	53 (46.1)
Post graduate	15 (13)
Marital status	
Single	48 (41.7)
MS relapses pattern	
Relapsing –remitting(RR)	84(73)
Secondary – progressive (SP)	31(27)
Occupation	
Unemployed	39 (33.9)
Student	13 (11.3)
MS duration(median)	5y(2-30)
History of allergy	
No	85(78.7)
Family history of MS	
Yes	14(12.5)
MS treatment	
Beta-interferon	25(23.3)
Sinoovex	26(24.2)
No treatment	7(6.5)

Table 2: High level Air pollution marker`s date characteristic

Year	M	CO Mean(SD)	M	No Mean (SD)	M	No2 Mean (SD)	M	Nox Mean (SD)	M	SO2 Mean (SD)	M	PM10 Mean (SD)
2009	8	4.8(2.048)	12	81.21(34.50)	10	53.50 (26)	2 5	94.99(18.25) 94.25(19.46)	10	36.5(14.5)	5	93.82(10.94)
2010	7 8 9	4.01(1.99) 4.00(1.3) 4.38(0.7)	10	99.32(43.73)	9	61.82(24.69)	4	85.45(20.22)	8	42.72(34.82)	8	85.24(43.90)
2011	10	2.89(0.3)	10	69.20(37.57)	12	63.23(41.29)	11	90.86(22.40)	10	34.86(16.33)	2	85.24(33.77)

Table 3: Air pollutant markers characteristics

	total				90			89			88		
	loc	**Mean**	**SD**	***P***	**Mean**	**SD**	***P***	**Mean**	**SD**	***P***	**Mean**	**SD**	***P***
co	1	3.04	.85		2.45	.45		3.33	.55		3.35	1.12	
	2	3.37	1.35		2.39	.48		3.14	.95		4.57	1.41	
	3	2.44	.58		2.33	.42		2.60	.50		2.40	.78	
	4	2.96	.67		2.74	.48		3.27	.87		2.85	.50	
	5	4.03	1.69		2.57	.38		5.15	1.56		4.36	1.65	
	Total	3.17	1.22	.000	2.50	.45	.188	3.50	1.27	.000	3.50	1.41	0.000
no2	1	49.63	17.95		34.44	9.80		59.06	20.13		55.37	11.80	
	2	52.95	18.62		61.07	26.76		53.76	14.21		44.02	4.98	
	3	33.47	10.07		30.71	4.86		32.79	9.46		36.91	13.71	
	4	52.24	19.94		53.47	30.49		46.91	9.45		56.34	13.96	
	5	28.46	18.62		35.88	29.08		21.32	7.62		28.18	9.15	
	Total	43.35	20.07	.000	43.11	25.13	.006	42.77	18.79	.000	44.16	15.36	0.000
no	1	67.98	37.12		50.78	18.03		74.73	42.53		78.44	41.94	
	2	55.22	31.96		33.28	17.61		70.02	38.28		62.35	25.62	
	3	32.55	16.48		29.24	11.35		30.36	15.79		38.05	20.88	
	4	37.70	22.66		28.00	13.31		42.38	26.87		42.74	24.08	
	5	89.27	42.84		71.21	27.78		1.01	54.92		95.08	38.65	
	Total	56.55	37.56	.000	42.50	24.43	.000	63.80	44.68	.000	63.3383	37.23	0.000
nox	1	1.18	52.78		85.75	22.27		1.34	62.15		1.34	52.91	
	2	1.08	35.42		94.83	17.78		1.24	47.71		1.06	30.34	
	3	65.72	21.14		59.13	15.29		63.15	22.32		74.87	23.34	
	4	90.53	32.36		82.09	27.96		89.87	32.43		99.64	36.46	
	5	1.18	44.30		1.07	46.33		1.23	53.07		1.23	33.12	
	Total	1.00	43.21	.000	85.88	31.65	.002	1.06	51.72	.002	1.07	40.91	.002
o3	1	28.93	16.94		22.79	11.69		33.96	21.28		30.03	15.92	
	2	29.72	19.13		28.35	9.19		45.97	26.74		26.78	24.24	
	3	23.00	16.97		22.36	11.60		22.36	16.65		24.22	22.09	
	4	27.02	12.74		24.02	8.32		23.74	11.80		33.30	15.61	
	5	21.03	14.12		12.92	5.44		24.16	20.37		24.64	8.65	
	Total	25.79	16.11	.127	22.41	10.49	.011	27.23	18.81	.195	27.81	17.74	.704
pm10	1	75.69	27.73		1.00	12.63		83.35	17.78		65.22	32.45	
	2	64.14	23.31		52.01	12.95		70.87	27.44		72.47	25.10	
	3	84.96	44.46		70.28	19.08		1.09	65.55		75.04	25.03	
	4	62.94	17.59		58.36	11.18		62.80	14.70		67.66	24.42	
	5	61.02	24.91		57.31	26.45		49.63	14.28		76.13	25.79	
	Total	69.48	30.41	0.003	61.12	20.40	.008	75.26	39.97	.002	71.28	26.17	.828
so2	1	44.23	14.28		38.64	5.11		46.56	21.04		47.48	11.36	
	2	26.83	16.01		45.46	16.11		20.93	6.53		17.21	7.73	
	3	23.78	19.68		13.90	2.00		26.21	11.07		31.91	31.31	
	4	20.67	9.61		26.92	3.09		21.52	8.53		18.26	11.22	
	5	23.59	7.41		23.05	3.43		23.87	5.17		23.85	11.66	
	Total	28.24	16.48	.000	29.44	14.29	.000	27.82	14.99	.000	27.67	19.57	.000

Time Series model

Various ARIMA models were tried and best model was determined as (p,d,q; 1,0,1) model between number of monthly relapses and the living place, although this model was not significant (*P*=0.3)(AR;*P*=0.000, MA;*P*=00.4).

Figure 1 shows monthly relapses in five different locations based on the air quality markers in Tehran during 3 years (March 2009- March 2011) (3y× 12m×5 location).

Higher relapse rate was observed during the winter and the following first month of the spring (see Figure 1). ARIMA significant model was determined as model (1, 0, 1), in the fifth place of residence (*P*=0.005) (Fig. 2).

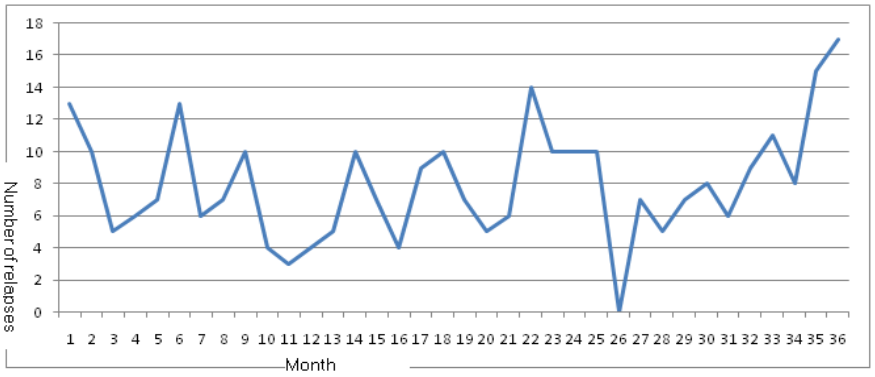

Fig. 1: Distribution of monthly MS relapses across 3 years

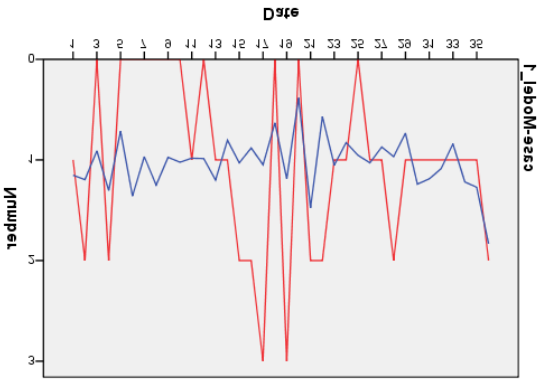

Fig. 2: ARIMA model in fifth location of residence between number of cases and NO2 level

Discussion

Our knowledge about MS relapse risk factors is limited. The air pollutants may inflict neurological diseases and may cause some neurological disorders. According to our findings, some air quality markers such as NO2 may be linked to MS relapse rate. The air quality markers and the pollutants are known as immune reactors in general (11, 12). Most studies demonstrated PM markers could affect neurological disorders such as stroke (13, 14). However, in one study, no consistent link to hemorrhagic or ischemic stroke was reported (15-18).

PM in higher levels of diesel exhaust emissions caused the rise of some proteins associated with neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease (19). Although, our findings did not show any link between PM10, ambient air gaseous inhalable matter and relapse rates in patients who suffered from MS, Oekenon and his collogues demonstrated that high PM10 level is linked to an increase in MS relapse rates(8). It is unclear as to whether NO2 contributed to some neurological affects such as stroke onset in short time exposure (13).

MS relapse rates were not correlated with CO levels and PM10 was correlated with MS attacks in non-users of beta-interferon. In our study, no link was observed between PM10, CO and MS relapse onset (8).Although, some elements in the air such as pollens create allergic effects on some people,

but in MS patients (20), considerably lower rate of allergy diseases were observed in our study (21-24). Vaccination also did not increase MS relapses (25, 26). A recent study illustrated a significant negative relationship between adenovirus and MS relapse rates in patients who were not treated by beta interferon (8). Our findings also did not provide any confirmatory evidence about the effect of viral infection on aggravation of MS symptoms.

Some other studies suggested that NO2 and NO caused neuro-inflammation. This fact can cause an increase in MS relapse rates. Since inaccurate relapse data can have a serious effect, therefore memory recall bias was minimized by elimination of uncertain data.

The air quality was different in different areas of Tehran. The pollutants moved to other areas by wind or other factors. This transfer of the pollutants changed the concentration levels in various locations and such effects were difficult to model. We demonstrated the most typical model in one of the explained locations using a monthly mean of NO2 concentration.

Our study anyway had some limitations such as low number of volunteers and some unknown factors including daily diet and physiological factors which were not taken into account in this study.

Conclusion

Although, there were some limitations, our study could demonstrate that the air pollutants can potentially be a risk factor for MS relapse.

Ethical considerations

Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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