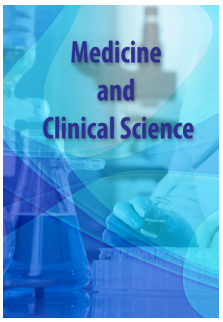
Medicine & Clinical Science

Original Article



Relationship Between Annual Airborne Pollen Levels and Occurrence of Parkinson Disease, Amyotrophic Lateral Sclerosis, Myasthenia Gravis, Multiple Sclerosis, Spinocerebellar Degeneration, Huntington's Disease, Shy-Drager Syndrome, Moyamoya Disease and Creutzfeldt-Jakob Disease Based on the National Registry Database of Specific Intractable Disease in Japan, 1974-2014: A Retrospective Study

Akira Awaya[1,2*] and Yoshiyuki Kuroiwa[3-5]

[1]*Dermatology & Epidemiology Research Institute (DERI), 4978 Totsuka-cho, Totsuka-ku, Yokohama, Kanagawa 244–0003, Japan*
[2]*Department of Genome System Science, Yokohama City University, Seto 22–2, Kanazawa-ku, Yokohama, Kanagawa 236–0027, Japan*
[3]*Department of Neurology and Stroke Center, University Hospital Mizonokuchi, Teikyo University School of Medicine, 5–1-1, Futago, Takatsu-ku, Kawasaki, Kanagawa 213–8507, Japan*
[4]*Department of Medical Office, Ministry of Finance, Japanese Government, 3–1-1, Kasumigaseki, Chiyoda-ku, Tokyo 100–8940, Japan*
[5]*Department of Neurology, Yokohama City University Graduate School of Medical Sciences, 3–9, Fukuura, Kanazawa-ku, Yokohama 236–0004, Japan*

Correspondence

Akira Awaya

Dermatology & Epidemiology Research Institute (DERI), 4978 Totsuka-cho, Totsuka-ku, Yokohama, Kanagawa 244–0003, Japan.

E-mail: awaya@home.email.ne.jp

Keywords:

specific intractable diseases, neurological intractable diseases, Parkinson disease, amyotrophic lateral sclerosis, Myasthenia Gravis, multiple sclerosis, spinocerebellar degeneration, Huntington's disease, Shy-Drager syndrome, moyamoya disease, Creutzfeldt-Jakob disease, Kawasaki disease, airborne pollen, pollen exposure, pollen levels, pollen-induced diseases, pollen diseases, patient-registry year, newly registered patients,

Tokyo Metropolitan, Sagamihara City.

- Received Date: 25 Dec 2022
- Accepted Date: 30 Dec 2022
- Publication Date: 31 Dec 2022

Abstract

Background: *In Japan, pollen counts increased between 1977 and 1987, including three peaks (1978-1980, 1982, 1984-1986) coinciding with triphasic Kawasaki disease (KD) outbreaks. Epidemiological findings have been then extensively accumulated that KD and related specific intractable diseases such as systemic vasculitis, collagen diseases, inflammatory bowel diseases, idiopathic dilated cardiomyopathy and further various cancers may be correlated to pollen exposure (PE).*

Methods and results: *To elucidate the effects of PE on outbreaks of neurological intractable diseases (NIDs), we evaluated the annual occurrence of disorders in relation to pollen counts using data from a national database. Specifically, we evaluated the occurrence of Parkinson disease (PD), amyotrophic lateral sclerosis (ALS), Myasthenia Gravis (MG), multiple sclerosis (MS), spinocerebellar degeneration (SCD), Huntington's disease (HUNTG), Shy-Drager syndrome, moyamoya disease and Creutzfeldt-Jakob disease (CJD). During 1975–2014, the 1984-86 peak of pollen scatter was the earliest big peak with which simultaneous increase in occurrence of PD, ALS, MG, MS, SCD and HUNTG coincided. Furthermore, simultaneous outbreaks of each NID coincided with subsequent ten peaks of pollen scatter till 2014. Our results showed statistically significant correlations for PD, ALS, MG, MS and SCD between the annual number of newly registered patients (nRPs) in the patient-registry year and annual pollen levels in the same patient-registry year. Significant correlations were also shown between the number of nRPs in the patient-registry year and annual pollen levels measured 3 years (PD), 6 years (PD, MG, MS, MMD), 9 years (PD, MS, MMD, CJD), 14 years (PD, CJD), and 16 years MG, MS, HUNTG and MMD before the patient-registry year.*

Conclusion: *We assume that cumulative effects of PE during a decade or more before the diagnosis of NIDs might possibly trigger onset of NIDs when cumulative effects of PE as environmental stress overwhelmed immunoreactive threshold.*

Introduction

In addition to genetic predisposition, environmental factors are thought to play a role in the pathogenesis of designated incurable specific intractable diseases (SIDs) and cancer and malignant tumors, and the possibility of microorganisms [1-4] and pollen [5-10] as candidate environmental factors has been reported.

Since 2003, when the author reported the finding that pollen may be the trigger of Kawasaki disease, which had been thought to be a disease involving some microorganism, the author has reported a total of four papers [11-14].

Citation: Awaya A, Kuroiwa Y. Relationship Between Annual Airborne Pollen Levels and Occurrence of Parkinson disease, amyotrophic lateral sclerosis, Myasthenia Gravis, multiple sclerosis, spinocerebellar degeneration, Huntington's disease, Shy-Drager syndrome, moyamoya disease and Creutzfeldt-Jakob disease Based on the National Registry Database of Specific Intractable Disease in Japan, 1974-2014: A Retrospective Study. Med Clin Sci. 2022; 4(4):8-18.

In 2018, the author found that the trigger for Takayasu disease, a designated incurable specific intractable diseases (SIDs), which is a vasculitis syndrome like Kawasaki disease, may also be caused by pollen, and the author has continued to report his opinion that the trigger for not only Kawasaki disease but also 40 designated intractable diseases and 24 types of cancer and malignant tumors may be pollen [5-10].

Regarding the relationship between the development of designated incurable diseases and pollen exposure, the author has previously reported data on vasculitis syndrome and collagen diseases such as SLE in the first report [5], on ulcerative colitis and interstitial pneumonia in the second report [6], and on dilated cardiomyopathy and polymyositis/dermatomyositis in the third report [9].

In this fourth report, we describe the relationship between the dynamics of disease onset and pollen dispersal variability in nine neurological intractable diseases (NIDs) followed over a 40-year period.

The total number of Japanese registered as having a designated intractable disease in Fiscal Year 2020 is 1,033,770. In terms of the number of people registered with designated intractable diseases other than neurological intractable diseases, inflammatory bowel disease, consisting of 140,574 people with ulcerative colitis and 47,633 people with Crohn's disease, accounted for the largest number of 188,207, followed by systemic lupus erythematosus (64,468) [data from the Center for Intractable Diseases, 15].

The target diseases of this study are nine neurological intractable diseases that are recognized as designated intractable diseases, which are broken down into the following disease names, and the number of people enrolled in these diseases is also described below [from data from the Center for Intractable Diseases, 16].

The breakdown of the neurological intractable diseases included in our analysis and the number of people enrolled in each were as follows: 142,375 people with Parkinson's disease (PD), 10,514 people with amyotrophic lateral sclerosis (ALS), 25,416 people with myasthenia gravis (MG), 21,437 people with multiple sclerosis (MS), 27,365 people with spinocerebellar degeneration (SCD), 950 people with Huntington's disease (HUNTG), 11,694 people with Shy-Drager syndrome (integrated into multiple system atrophy since 2003) , 13,894 people with Moyamoya Disease (MMD), and 481 people with Creutzfeldt-Jakob Disease (CJD) or Prion disease.

Recent technological developments have made possible the comparison of microbiota between groups, and research into the human microbiome is at the forefront of science. More recent research has identified the strong influence of the human gut microbiota on brain physiology and homeostasis via immune, neural, endocrine and metabolic pathways. In fact, gut microbiota alterations have been found in PD. Nielsen SD, et al. examined the mechanism of pathophysiology of PD with a specific interest in the role of the gut microbiota and the retrograde transport of the pathology from the gut to the brain [17].

Disruption to the bidirectional communication between the gut and the brain has been linked to several disorders including PD and MS. Inflammatory stress via pollen exposure might be a trigger for the onset of PD, disrupting inflammatory factors to mediate communication between the gut and the brain, travelling between the central, autonomic, and enteric nervous system.

The author investigated "the correlation between resistance or susceptibility to hay fever and the presence or absence of moles" and reported the finding that "the ability to form moles is a phenotype (predisposition) for resistance to allergic diseases such as pollinosis" [18]. He further found that the skin condition and appearance of patients with PD and hard of hearing people seem to be soft and glowing, and they have less or almost no moles in the face and neck. And he reported that incidence rate of pollinosis in both PD patients and hard of hearing people is high and suggested that they are susceptible to pollens and highly reactive to pollen exposure [19-25].

Multiple sclerosis (MS) is a neurological intractable disease caused by autoimmune inflammation that results in demyelinating foci in the central nervous system. Concerned about the rapid increase in the number of MS patients in Japan, Takashi Yamamura's group at the National Center of Neurology and Psychiatry has been examining the possibility that changes in the gut microbiota may be related to changes in lifestyle, especially due to westernization of diet. Yamamura et al. identified the gut microbiota species that decrease in relapsing-remitting MS and exacerbate secondary progressive MS, and elucidated the mechanism by which the gut microbiota exacerbate neuroinflammation [26]. In MS as well as PD, inflammatory stress via pollen exposure could be a trigger for the onset of MS, via disruption of inflammatory factors to mediate the bidirectional communication between the gut and the brain communication.

The author has reported on FTS (serum thymic factor=STF, Zn-free thymulin) nonapeptide, a serum thymic factor that very strongly prevents death of animals in experimental allergic encephalomyelitis (EAE) in guinea pigs and rats, an experimental animal model of MS. The author later reported that this synthetic FTS nonapeptide strongly suppressed pollen-induced allergic rhinitis in guinea pigs at one-thousandth the dose of steroids [8,10,25].

Since both PD and MS are presumed to involve host immunological responses to pollen exposure in their pathogenesis, we have conducted an epidemiological analysis of these diseases and report the results.

In this research, we examined the relationship between upward peaks of airborne pollen (AP) released in the Bunkyo-City area of Tokyo, in the whole area of Tokyo Metropolitan, and in Sagamihara City of Kanagawa Prefecture in relation to the increase in the annual number of newly registered patients (nRPs) during 1974-2014. The aim of our study was to evaluate the associations between AP exposure peaks and the occurrence of immune-related, principal 40 SIDs including NID, vasculitis syndrome, connective tissue diseases, gastroenterological diseases and so on in Japan. We hypothesized that these immune-related diseases might belong to the class of pollen-induced diseases (PIDs), or “pollen diseases,” because so far accumulated data have suggested that these conditions may be triggered when susceptible patients receive AP exposure that exceed the pollen-responsive threshold of the individuals, and reach a starting line to development of diseases.

The relationship between the onset of PD and pollen exposure is briefly described by the author in a report article discussing the relationship between the onset of cancer and pollen exposure [8], and the author presents some data on the relationship between the onset of MG and pollen exposure in a report article discussing the relationship between the onset of muscle incurable diseases and pollen exposure [7].

Materials and methods

Since 1974, the Japanese governmental authority (JIDRF) has assigned certificates to SID patients to support their treatment financially following registration in a national database [15,16]. The homepage of the JIDRF reports the "numbers of recipient certificates issued for specific disease treatment" based on registration beginning in 1974 or 1975, 1983 or 1984, and so on until 2014. The data show the number of presently RPs in the current fiscal year (April 1 to March 31) as well as the number of nRPs relative to the previous fiscal year for all the major SIDs. These increments could be negative if the number of presently RPs in the present fiscal year was smaller than that in the previous fiscal year, which occurs occasionally. This study was performed in accordance with the ethical principles for medical research outlined in the Declaration of Helsinki 1964 and subsequent revisions (https:// www.wms.net/).

Data on AP release were provided by Dr. Yozo Saito, Dr. Hiroshi Yasueda, and Professor Norio Sahashi. Dr. Saito gathered the AP data from data at the research unit in the Tokyo Medical Dental University Graduate School of Medicine, Bunkyo-City, Tokyo, and Dr. Yasueda surveyed AP data based on the research at the National Hospital Organization Sagamihara National Hospital, Sagamihara, Kanagawa [6-10]. The AP data in Tokyo Metropolis were collected from 12 sites in Tokyo and were donated by Mr. Hiroshi Kaneko. The AP data were downloaded after administrative information disclosures from the website of the Tokyo Metropolitan Institute of Public Health [6-10, 27]. In the present study, data of numbers of SID patients in all the Japan were imported into tables in Microsoft Excel. This data was used to create figures of line graphs for each SID. These figures represent annual numbers of presently RPs as well as nRPs, and the scattered pollen counts in three areas in Japan (the Bunkyo-City area of Tokyo, the whole area of Tokyo Metropolitan, and Sagamihara City in Kanagawa). A correlation analysis was performed for each SIDs, to evaluate the association between the annual number of nRPs in each patient-registry year "x" during 1974–2014, and the annual amount of AP levels in Tokyo and Sagamihara, measured in the same year as the patient-registry data. A correlation shift analysis was also performed between the annual number of nRPs in each patient-registry year "x" between 1975 and 2014 and the annual AP levels in both cities measured "α" years prior to the patient-registry year "x"("α"=1–20). Correlation coefficients and p values were calculated using the Excel function PEARSON via the method described in the brochure http://imnstir.blogspot.com/2014/04/p.htm. A statistically significant positive correlation was defined as $p<0.05$. Marginally significant associations that indicated a possible positive tendency ($0.05\leq p\leq 0.10$) were also reported for reference.

Results

Occurrence of upward peaks in the line graphs of the annual number of nRPs for nine NID in relation to the annual levels of AP scatter

Graphs were created simultaneously plotting the number of patient (both presently and newly RPs) cases of neurological intractable diseases and the number of pollen dispersal for the period 1985–2014 (Figures 1–9). The five line graphs in our figures for nine neurological intractable diseases consist of two line graphs visualizing the annual patient-registry data for presently RPs and nRPs, and three line graphs visualizing the annual amount of AP scatter measured in three geographical areas. As shown in our line graphs, the amount of cedar pollen scatter in both Sagamihara City and Bunkyo-City started to increase during 1977–87, showing three distinct peaks (1978–80, 1982, 1984–86). Fundamentally, steady phasic increases in annual numbers of both presently and nRPs concurrent with a consecutive series of 13 upward AP peaks (1978–80, 1982, 1984–86, 1988, 1990–91, 1993, 1995, 1997–98, 2000–03, 2005, 2008–09, 2011 and 2013) were observed for nine NID (Table1), in the same way as already reported in our previous articles on SIDs or cancers [6–10]. Below described findings suggest that the occurrence of each NID appeared to start simultaneously and to increase concurrently with pollen scatter in Japan from the latter half of the 1970s until the early 2010s.

The increase in newly RPs in PD, ALS, MG, MS, SCD, and HUNTG, especially in HUNTG patients, was remarkable during the early years of the rapid increase in pollen counts, especially in 1984–86.

At that time, the largest amount of pollen dispersal ever occurred in 1995, and then around 1997, PD, ALS, MG, MS, HUNTG, and CJD were included in the list of diseases with notable increases in newly RPs.

Although a steady increase in newly RPs in 2000–03 occurred in all neurological intractable diseases, the annual increase in newly RPs in ALS, MG, MS, SCD, HUNTG, and MMD was particularly significant.

Diseases with a slightly greater degree of increase in newly RPs in the period around 2008–09, after the largest pollen dispersal on record in 2005 at that time, were PD, MG, SCD, and CJD.

After 2005, the increase in newly RPs in patients with various neurological intractable diseases in 2011, when the pollen count was the second highest, and 2014 was very pronounced except for CJD. The preemergence dispersal of cedar pollen that occurred in the fall of 2010, a very hot year, was seen to have increased the number of newly RPs in CJD in 2010.

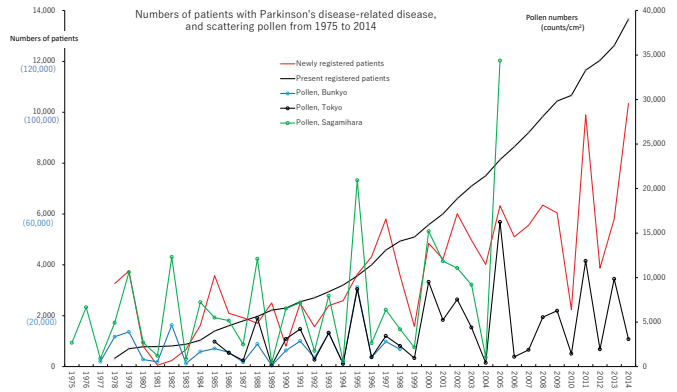


***Figure 2**. Numbers of patients with Parkinson's disease-related disease, and scattering pollen from 1975 to 2014.*
The line graphs for Parkinson's disease-related disease representing numbers of present registered and newly registered patients in each year, as well as the amount of pollen scattered in Bunkyo-ku, Metropolitan Tokyo and Sagamihara city during the period from 1975 to 2014. Numbers of patients are shown on left axes whose scales are black reduced numbers to newly registered patients and (blue actual numbers) to present registered patients. Pollen numbers are shown on right axes whose scales are counts/cm².

DOI: *10.33425/2690-5191.1067*

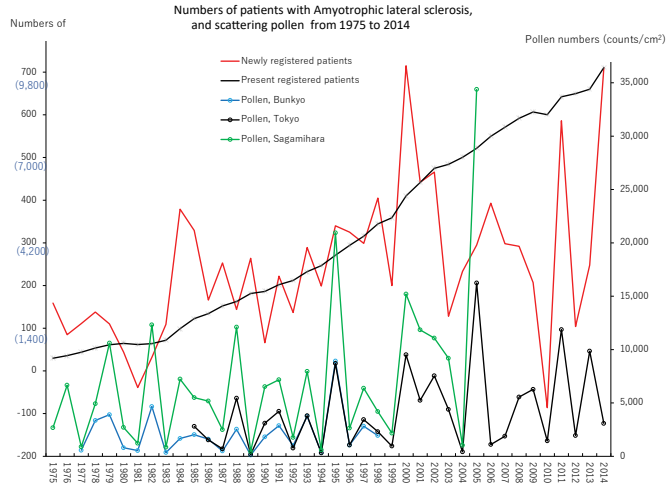


Figure 2. *Numbers of patients with amyotrophic lateral sclerosis, and scattering pollen from 1975 to 2014.*
The line graphs for amyotrophic lateral sclerosis representing numbers of present registered and newly registered patients in each year, as well as the amount of pollen scattered during the period from 1975 to 2014. Following explanation is the same as in Figure 1, so to be seen there.

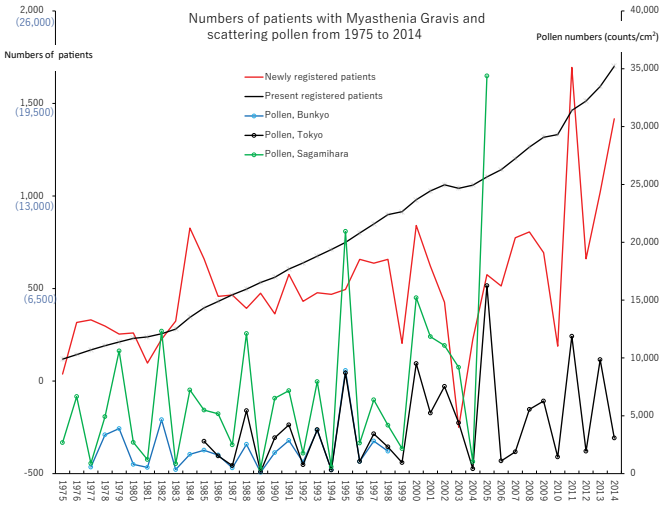


Figure 3. *Numbers of patients with Myasthenia Gravis, and scattering pollen from 1975 to 2014. The line graphs for Myasthenia Gravis representing numbers of present registered and newly registered patients in each year, as well as the amount of pollen scattered during the period from 1975 to 2014. Following explanation is the same as in Figure 1, so to be seen there.*

The registration of the number of patients with designated intractable diseases includes the number of patients with the disease from January to March, which is the last month of the fiscal year, in the following calendar year. The increase in the number of patients induced by the advance dispersal of cedar pollen in autumn after very hot summer and the number of patients from January to March may have added up to a large number of cases reported in the fiscal year before the year with high pollen counts (Table 1).

Statistical relationships between the number of nRPs in each patient-registry year and AP levels measured in the same year or prior to the patient-registry year

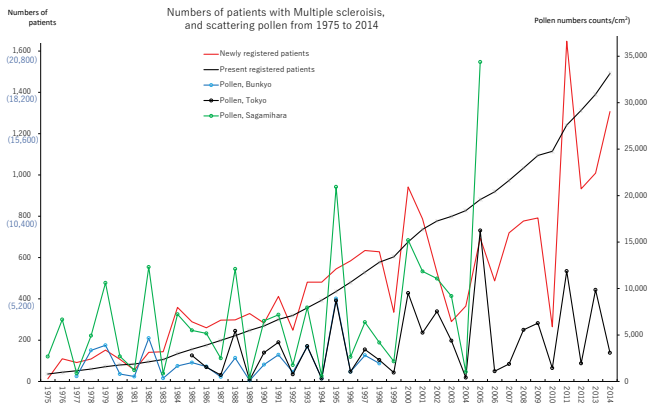


Figure 4. *Numbers of patients with Multiple sclerosis, and scattering pollen from 1975 to 2014.*
The line graphs for Multiple sclerosis representing numbers of present registered and newly registered patients in each year, as well as the amount of pollen scattered during the period from 1975 to 2014. Following explanation is the same as in Figure 1, so to be seen there.

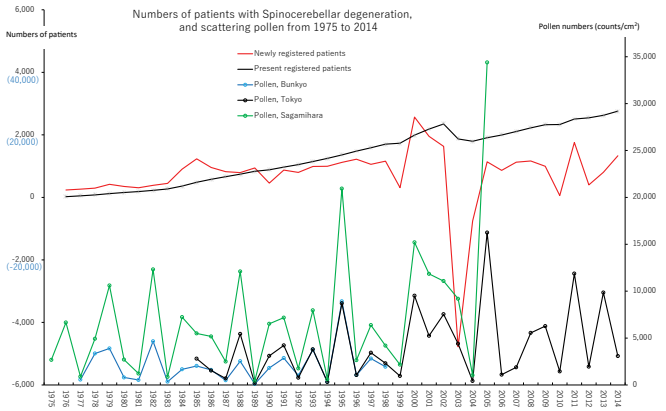


Figure 5. *Numbers of patients with spinocerebellar degeneration, and scattering pollen from 1975 to 2014.*
The line graphs for spinocerebellar degeneration representing numbers of present registered and newly registered patients in each year, as well as the amount of pollen scattered during the period from 1975 to 2014. Following explanation is the same as in Figure 1, so to be seen there.

We examined the statistical correlations between the annual number of newly registered in each patient-registry year "x" ("x"=1975–2014) for nine neurological intractable diseases and the corresponding annual AP levels in Tokyo and Sagamihara, measured in the same year as the patient-registry data "x" as well as measured with a lag of "α" years before the patient registry year "x" ("α"=1–20).

Statistically significant positive correlations were indicated by p values <0.05 (shown in red in Table 2), and marginal associations were indicated by p values between 0.05 and 0.100(shown in green). Reference data of associations with p values slightly greater than p=0.10 in one city (Tokyo or Sagamihara) and the corresponding p values of another city are also indicated. Only p values in "α=0–16" are shown which were gotten by this calculation in this Table 2.

DOI: *10.33425/2690-5191.1067*

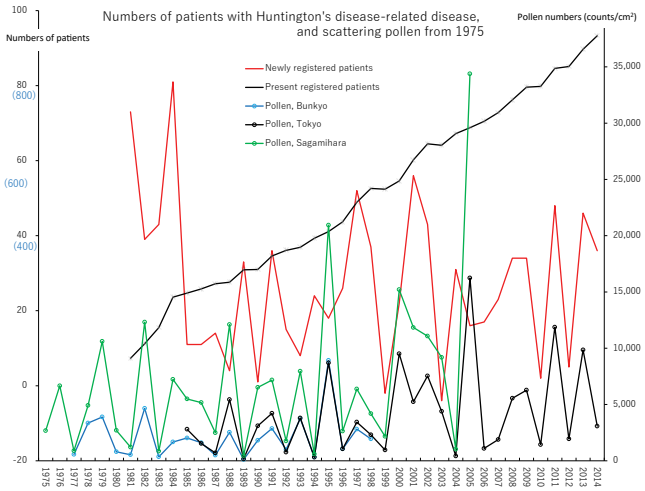


Figure 6. *Numbers of patients with Huntington's disease-related disease, and scattering pollen from 1975 to 2014.*
The line graphs for Huntington's disease-related disease representing numbers of present registered and newly registered patients in each year, as well as the amount of pollen scattered during the period from 1975 to 2014. Following explanation is the same as in Figure 1, so to be seen there.

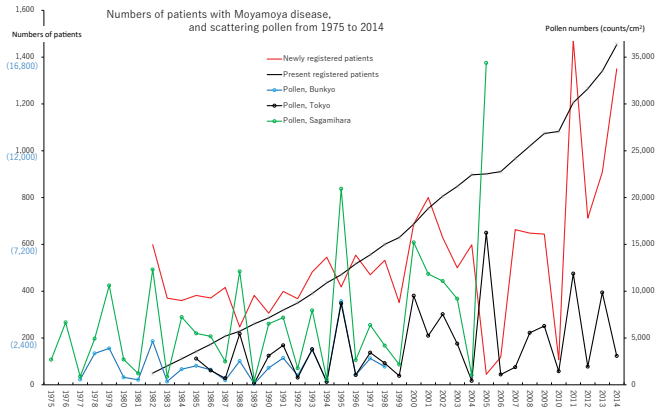


Figure 8. *Numbers of patients with Moyamoya disease, and scattering pollen from 1975 to 2014. The line graphs for Moyamoya disease representing numbers of present registered and newly registered patients in each year, as well as the amount of pollen scattered during the period from 1975 to 2014. Following explanation is the same as in Figure 1, so to be seen there.*

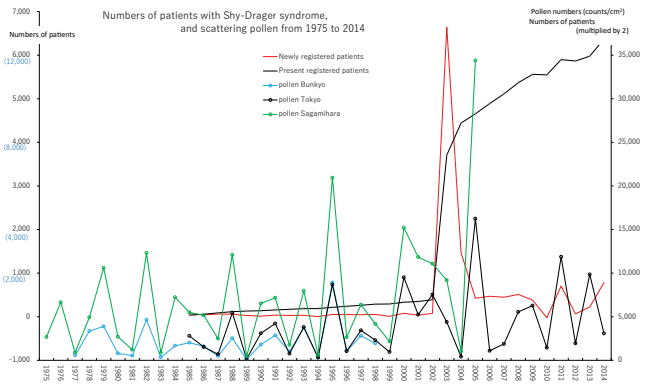


Figure 7. *Numbers of patients with Shy-Drager syndrome, and scattering pollen from 1975 to 2014. The line graphs for Shy-Drager syndrome representing numbers of present registered and newly registered patients in each year, as well as the amount of pollen scattered during the period from 1975 to 2014. Following explanation is the same as in Figure 1, so to be seen there.*

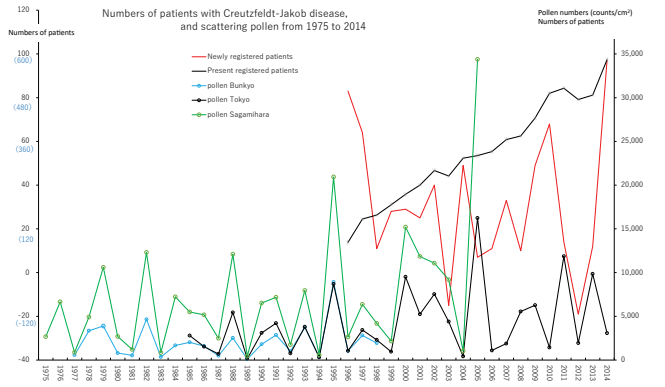


Figure 9. *Numbers of patients with Creutzfeldt-Jakob disease, and scattering pollen from 1975 to 2014.*
The line graphs for Creutzfeldt-Jakob disease representing numbers of present registered and newly registered patients in each year, as well as the amount of pollen scattered during the period from 1975 to 2014. Following explanation is the same as in Figure 1, so to be seen there.

Our results showed statistically significant correlations between [the number of nRPs in the patient-registry year "x" abbreviated as Nos in "x" below in this column] and the amount of AP exposure measured in Tokyo, in the same year as the patient-registry year 0 for PD, ALS, MG, MS and SCD. Similarly, significant correlations were shown for PD, MS and SCD between Nos in "x" and AP exposure measured in Sagamihara, in the same year as the patient-registry year 0. Regarding PD, we found significant correlations between Nos in "x" and AP exposure measured in Tokyo, 3, 6, 9 and 14 years prior to the patient-registry year "x", and significant correlations between Nos in "x" and AP exposure measured in Sagamihara, 6 and 9 years prior to the patient-registry year "x". As to MG, MS and MMD, we also found significant correlations between Nos in "x" and AP exposure measured in both Tokyo and Sagamihara, 6 years prior to the patient-registry year "x". In 9 years prior to the patient-registry year "x", we found significant correlations between Nos in "x" and AP exposure measured in Sagamihara for MS, and in both Tokyo and Sagamihara for MMD and CJD. In 14 years prior to the patient-registry year "x", we found significant correlations between Nos in "x" and AP exposure measured in both Tokyo and Sagamihara for CJD. In 16 years prior to the patient-registry year "x", we found significant correlations between Nos in "x" and AP exposure measured in both Tokyo and Sagamihara for CJD. There were many positive tendencies observed in Table 1. For MS, 9 and 11 years prior to the patient-registry year "x" in Tokyo or both cities. For ALS, 6 and 16 years prior to the patient-registry year "x" in both cities or Sagamihara. For MG, 9 and 11 years prior to the patient-registry year "x" in both cities or Tokyo. For HUNTG, 6 years prior to the patient-registry year "x" in Tokyo and Sagamihara. For SDS, 3 or 8 years prior to the patient-registry year "x" in Tokyo or Sagamihara.

DOI: *10.33425/2690-5191.1067*

***Table 1**. Peaks of occurrence of SIDs in Japan between 1974 to 2014*

Figure. No	Figure1	Figure2	Figure3	Figure4	Figure5	Figure 6	Figure7	Figure 8	Figure 9
Years of pollen peaks and next years	PD	ALS	MG	MS	SCD	HUNTG	SDS	MMD	CJD
1978-79, 1980	○	○	○	○	○	*	*	*	*
1982, 1983		○	○	○	○	○1981	*	○	*
1984~86, 1987	○	○	○	○	○	○	○	○	*
1988, 1989	○	○	○	○	○	○	○	○	*
1990-91, 1992	○	○	○	○	○	○		○	*
1993, 1994	○	○	○	○	○	○		○	*
1995, 1996	○	○	○	○	○	○	○	○	○
1997-98	○	○	○	○	○	○	○	○	○
2000~03	○	○	○	○	○	○	○	○	○
2005, 2006	○	○	○	○	○	○2004		○2004	○2004
2008~09	○	○	○	○	○	○	○	○	○2007
2011, 2012	○	○	○	○	○	○	○	○	○2010
2013, 2014	○	○	○	○	○	○	○	○	○

*not registered. The peaks of 1981, 2004, 2007 and 2010 are to be considered as the contribution of not so little patients numbers based on fore-running pollen scatter after hot summer in Sep. to Dec. and following seasonal pollen scatter in Jan. to Mar. in the fiscal years.

Table 2. *Statistical relationships between the number of newly RPs in each patient-registry year and AP levels measured in the same year or prior to the patient-registry year.*

A correlation analysis between the annual number of newly registered patients in each patient-registry year "x" ("x"=1975-2014), and the annual amount of airborne pollen levels in Tokyo (T) and Sagamihara (S), measured in the same year as the patient-registry year "x", and measured "α" years before the patient-registry year "x" ("α"=1-20) , for Parkinson's disease, amyotrophic lateral sclerosis, Myasthenia Gravis, multiple sclerosis, spinocerebellar degeneration, Huntington's disease, Shy-Drager syndrome, moyamoya disease and Creutzfeldt-Jakob disease.
In this Table, the data in the case of "α" =1-16 are shown.

		Figure 1	**Figure 2**	**Figure 3**	**Figure 4**	**Figure 5**	**Figure 6**	**Figure 7**	**Figure 8**	**Figure 9**
α		PD	ALS	MG	MS	SCD	HUNTG	SDS	MMD	CJD
0	T	0.003914	0.039597	0.030903	0.002563	0.004405				
	S	0.007999	0.060249	0.207568	0.005377	0.014706				
1	T	0.327408								
	S	0.109343								
2	T	0.225851			0.538427					
	S	0.073203			0.161431					
3	T	0.019918			0.103135			0.054992	0.16367	
	S	0.080057			0.102593			0.193039	0.409409	
4	T									
	S									
5	T					0.255522				
	S					0.142673				
6	T	0.006508	0.099972	0.009246	0.007155		0.050796		0.010366	
	S	0.005843	0.074539	0.000463	0.000122		0.093035		0.000143	

DOI: *10.33425/2690-5191.1067*

		Figure 1	Figure 2	Figure 3	Figure 4	Figure 5	Figure 6	Figure 7	Figure 8	Figure 9
7	T									
	S									
8	T							0.243444	0.811798	
	S							0.053713	0.164504	
9	T	0.014327	0.167951	0.063048	0.064881				0.025561	0.010698
	S	0.023824	0.101994	0.06905	0.043703				0.014819	0.004394
10	T									
	S									
11	T			0.063968	0.069441				0.075981	
	S			0.11504	0.088618				0.146028	
12	T				0.231507					
	S				0.138723					
13	T						0.144962			
	S						0.2614			
14	T	0.038062	0.215796	0.15009	0.199931				0.177274	0.010035
	S	0.174959	0.193874	0.16704	0.200501				0.146589	0.025555
15	T									
	S									
16	T	0.13153	0.120923	0.040507	0.048129		0.044923		0.021316	
	S	0.16372	0.051592	0.019352	0.022723		0.017441		0.008755	

p values<0.05 are in red color. 0.05< p values <0.10 are in green color.
Numerical data only for reference are also shown. Other data are deleted to blank.

Discussion

Once again, the results of the correlation analysis between the dynamics of the onset of neurological intractable diseases such as PD and MS, which have been followed for 40 years since the 1970s, and the variation in pollen exposure are generally the same as those reported in the previous three reports on designated intractable diseases and the three reports on cancer and malignant tumors.

It is an epidemiological fact that pollen dispersal, a natural weather phenomenon or a life phenomenon in the plant kingdom with an annual cycle, is a common trigger that specifies, controls, or influences the dynamics of various human diseases, including KD and 40 designated incurable diseases and 24 types of cancer and malignant tumors that the author has investigated, including unpublished diseases. However, since the time of the author's 2003 KD report, this epidemiological fact has not received attention from expert researchers, and no research follower seems to have emerged yet.

In PD, ALS, MG, MS and SCD, we performed our previous 20-year displacement analysis work looking at the correlation between newly RPs and the amount of pollen exposure. The results showed that not only was there a significant correlation between newly RPs and pollen exposure in the year of registration, but also between newly RPs and pollen exposure 6 years prior to the year of registration, as was previously reported for ulcerative colitis (UC), Crohn's disease (CD), primary biliary cirrhosis (PBC), interstitial pneumonia (IP), and idiopathic dilated cardiomyopathy, polymyositis/dermatomyositis, granulomatosis with polyangiitis, periarteritis nodosa [6,7].

The increase in newly RPs is estimated to be greater when a mass pollen outbreak or an equivalent large pollen outbreak occurs both in year 0 of registration and 6 years prior to registration, for example, when the mass pollen outbreak overlaps in each pair, as in 1978 and 1984, 1995 and 2001, 1982 and 1988, and 2005 and 2011.

PD was not only triggered by pollen exposure received in the year of registration, but also significantly correlated with pollen exposure received 6 years prior to the year of registration.

For the increase in newly RPs in PD patients, significant correlations were found with pollen exposure 3, 9, and 14 years ago, as well as 6 years before the year in which the onset of disease was registered.

For the increase in newly RPs in patients, significant correlations were found with pollen exposure 9, and 16 years ago, as well as 6 years before the year in which the onset of disease was registered. In Japan, it is necessary to examine whether we can consider cedar pollen to be dispersed in large amounts at intervals of about 6 years.

In other countries, there may be some differences from the Japanese phenomenon due to differences in latitude, etc. However, considering the commonality of plant physiology, it may be possible to predict the existence of a correlation between pollen dispersal phenomenon and human disease development triggered by pollen exposure. We look forward to initiating research in other countries.

Now that the author has recognized the principle of disease onset, that pollen exposure may be a trigger for the onset of

various designated intractable diseases, cancers, and malignant tumors, he would like experts to find the results of repeated exposure to pollen in experimental animal models of each disease, which accelerates disease onset and clearly and strongly manifests symptoms [6–10, 28].

There are animal models used in aging research, such as the accelerated aging model mouse SAM. Such aging animal models could be strongly exposed to pollen to accelerate aging in accelerated experiments, or cellular aging could be observed in cellular experimental systems in which pollen components are added to cells. The first priority is to quickly clarify that avoiding pollen exposure is effective in increasing the immortality of SAMs and aging developing cells by such experimental medical methods.

It remains to be clarified how the cellular signal emission that occurs in the experimental animal model system of PD after massive pollen exposure leads to the abnormal attraction that occurs in the metabolic system of dopamine (DA)-producing cells, substantia nigra, a process that is still awaited.

For example, it may be necessary to examine whether pollen exposure causes a decrease in pigment cell, melanocytes activity.

The author has been thinking that pigment cells regulate mast cells, which are involved in the onset of allergy. We would like to know how the signals emitted by the pollen-sensitive cells are transmitted to the pigment cells and how they are antagonized (or weakened) by the oxidative stress suppression ability of the pigment cells. We hope that experimental medicine will be able to find out in what form the signals emitted by pollen-exposed cells are transmitted to the brain when the substantia nigra is damaged, which is a major factor in the development of PD.

Human pollen exposure begins after birth. Human organs, tissues, and cells slowly experience inflammation and aging under the influence of foreign environmental factors such as pollen, and pollen acts on the body as a causative agent of future disease onset, and the body enters an undiseased state.

As the individual gets older and is exposed to pollen every year, pollen reactivity increases, and when the individual's pollen reactivity exceeds a threshold, a large amount of pollen exposure becomes the proximate trigger, and the process of disease onset begins at the starting point of the disease process.

In the case of KD, the total incidence rate of 0 and 1 year old infants is 50%, and the elapsed time required from pollen exposure to disease onset is very short [13].

We suppose that it is important to gaze at and to elucidate the initial phase of common cellular responses induced by pollen. When human bodies are exposed to pollen, the pollen as the environmental stress, may facilitate intra-cellular processing and cellular responses. The environmental stress of pollen exposure must be a common trigger for the development of diseases and highlights the real and essential issues of life phenomena, and the early response of living cells in earlier period of pollen exposure should be elucidated. When the initial phase of the disease onset is triggered by pollen exposure, the pollen cells act on organs, tissues, and cells in the human body, and are supposed to enter the steps of cellular senescence or cellular degradation [10]. It might cause the condition of the patient who has not become ill yet, and then induces the progression process to the onset of multiple individual diseases.

We would like to recommend lifestyle habits that can prevent the early onset of designated intractable diseases due to pollen exposure and the worsening or recurrence of symptoms during treatment after disease onset due to pollen exposure, as well as lifestyles that can reduce the incidence of diseases and ensure longevity.

To avoid pollen exposure as much as possible is important for the purpose of preventing the aggravation of symptoms or recurrences, as well as the co-occurrence of other diseases. Pollen-avoidance prophylactic measures include the precaution of wearing safety masks, goggles, and transparent shields during pollen peaks from the early postnatal period, and of installing air cleaners in homes, particularly during seasons with large amounts of pollen release in spring and with small amount of forerunning pollen release of cedar pollen in September to December before next spring. These measures may help avoid or delay the first onset of neurological intractable diseases (NIDs), including those in young infants who have a potential risk of developing immune-mediated diseases. To prevent the development of NIDs, especially to delay the age of onset in people with NIDs families, it is important to reduce cumulative pollen reactivity and extend the time to onset by reducing annual pollen exposure. For this reason, it will be necessary to maintain the above-mentioned lifestyle of wearing masks throughout the year, and to install pollen-cutters. In addition, we suggest that the application of pollen allergen immunotherapy to reduce pollen reactivity at the level of practical medical care and careful tasting of pollen-containing health foods might be attempted for longevity [29].

The author has reported the correlation between seasonal influenza epidemics and pollen exposure [30], and the association between SARS-CoV-2 outbreak in Wuhan, China and pollen exposure [31–33]. Unlike microorganisms that originally nest (reside or coexist) in human animals, pollen is a substance derived from the plant kingdom and is an exogenous environmental factor, and its potential as a trigger for disease onset is even greater.

Acknowledgments

Akira Awaya deeply appreciates Mr. Koichi Iwata for his elaborate and diligent graphing work and correlation analysis. He also thanks Mr. Eiji Yamada for his technical support.

Conflicts of interests

The authors declare no conflict of interest in the preparation of this article.

Funding

The authors have never had an opportunity of receiving any research fund in relation to this research.

References

1. Tan AH, Lim SY, Lang AE. The microbiome-gut-brain axis in Parkinson disease - from basic research to the clinic. Nat Rev Neurol. 2022;18(8):476-495.
2. Glassner KL , Abraham BP, Quigley EMM. The microbiome and inflammatory bowel disease. J Allergy Clin Immunol. 2020;145(1):16-27.
3. Kenji Ishitsuka. Diagnosis and management of adult T-cell leukemia/lymphoma.Semin Hematol. 2021;58(2):114-122. .
4. Poorolajal J, Moradi L, Mohammadi Y, Cheraghi Z, Gohari-Ensaf F. Risk factors for stomach cancer: a systematic review and meta-analysis. Epidemiol Health. 2020;42:e2020004.
5. Awaya A. Development of many so-called autoimmune diseases

including various vasculitis syndromes may be commonly triggered by pollen exposure. Jacob J Aller Immuno. 2018; 5: 26.

6. Awaya A, Kuroiwa Y. A Retrospective study on the relationship between annual airborne pollen levels during four Decades of 1975- 2014 and annual occurrence of ulcerative colitis, Crohn's disease, primary biliary cirrhosis, fulminant hepatitis, severe acute pancreatitis, interstitial pneumonia, amyloidosis, based on the National Registry Database of Specific Intractable Diseases in Japan. Arch Epidemiol Public Health. 2019;1:112
7. Awaya A, Kuroiwa Y. Relationship Between Annual Airborne pollen Levels (1974–2014) and the Occurrence of Idiopathic Dilated Cardiomyopathy, Myasthenia Gravis, Polymyositis/ Dermatomyositis, and Vasculitis Syndrome Based on the National Registry Database of Specific Intractable Disease in Japan: A Retrospective Study. Austin J Clin Immunol. 2022; 8(1):1048
8. Awaya A, Kuroiwa Y. The Relationship between Annual Airborne Pollen Levels and Occurrence of All Cancers, and Lung, Stomach, Colorectal, Pancreatic and Breast Cancers: A Retrospective Study from the National Registry Database of Cancer Incidence in Japan, 1975–2015. Int. J. Environ. Res. Public Health 2020;17:3950.
9. Awaya A, Kuroiwa Y. 40 Specific Intractable Diseases and 24 Types of Cancer and Malignancies as Well as Kawasaki Disease May be Triggered by Pollen. Arch Environ Sci Environ Toxicol. 2020;3:130.
10. Awaya A, Kuroiwa Y. Relationship Between Annual Airborne Pollen Levels And Occurrence Of Thyroid, Skin, Esophagus, Kidney And Ovary Cancers, And Leukemia, Multiple Myeloma And All Cancers: A Retrospective Study Based On The National Registry Database Of Cancer Incidence In Japan, 1975–2015. Med Clin Sci. 2022;4(4):1-11
11. Awaya A, Sahashi N. The etiology of Kawasaki disease: does intense release of pollen induce pollinosis in constitutionally allergic adults, while constitutionally allergic infants develop Kawasaki disease?. Biomedecine & pharmacotherapie. 2004;58(2):136-140.
12. Awaya A, Murayama K. Positive correlation between Japanese cedar pollen numbers and the development of Kawasaki Disease. Open Allergy J. 2012;5:1-10.
13. Awaya A, Nishimura C. A combination of cross correlation and trend analyses reveals that Kawasaki disease is a pollen-induced delayed-type hyper-sensitivity disease. Int J Environ Res Public Health. 2014;11(3):2628-2641.
14. Awaya A. Suppressive influence of seasonal influenza epidemic on Kawasaki disease onset. Nihon Rinsho Meneki Gakkai Kaishi. 2016;39(6):528-537.
15. Brochure downloaded from HP of Japan Intractable Diseases Research Foundation, http://www.nanbyou.or.jp/entry/141. Japanese.
16. The data downloaded from http://www.nanbyou.or.jp/ entry/1356 in http://www.nanbyou.or.jp/entry/141. Japanese.
17. Nielsen SD, Pearson NM, Seidler K. The link between the gut microbiota and Parkinson's Disease: A systematic mechanism review with focus on α-synuclein transport. Brain Res. 2021;1769:147609.
18. Awaya A, Watanabe K, Kato S. Individuals exhibiting conspicuous nevi (lentigo simplex) are resistant to allergic rhinitis/conjunctivitis (pollinosis), but those who do not show increased susceptibility to pollinosis. Microbiol Immunol. 2003;47(1):101-3.
19. Awaya A. On the report from Sweden that fewer melanocytic nevi found in children with active atopic dermatitis -In pursuit of cutting open the paradigm of melanocyte immunology-. Allergy & Immunology. 2005;12(18):1214-1217.
20. Awaya A. Urgent effort of the start of the study to demonstrate many existence of pollen-induced diseases (PID). Clinics in allergy. 2004;24:376-379. [In Japanese].
21. Awaya A. A practice of the hygiene to hold progress of Parkinson's disease in check. Neuroimmunology. 2005;13(1):90.
22. Awaya A. A device and practice of the hygiene to hold progress hard to hear in check of the person with hearing loss. Supplement to Journal of Epidemiology. 2006;16(1):184.
23. Awaya A. A device and practice of the hygiene to suppress progress hard to hear of the person with hearing loss. Neuroimmunology. 2007;15(1):102.
24. Awaya A. In the group of patients with Parkinson disease, allergic prevalence is high, and the ratio of person hard of hearing is high. Supplement to Journal of Epidemiology. 2008;18(1):151.
25. Akira A. The important role of melanin synthesis and metabolism systems in biodefense mechanisms, and development as foods with function claims of substances having equal bioactivities to a lead compound FTSnonapeptide in drug innovation. Cell. 2017;49:676–677. [In Japanese].
26. Daiki Takewaki , Takashi Yamamura. Gut microbiome research in multiple sclerosis. Neurosci Res. 2021;168:28-31.
27. http://www.tokyo-eiken.go.jp/. Tokyo Metropolitan.
28. Awaya A. Proposal for construction of test and evaluation method in basic research and clinical study of medicines considering the effect of pollen exposure. Res Drug Interact. 2020;44:1–8.
29. Awaya A. Medicinal compositions for cancers and intractable diseases. Tokkai 2021-80252 laid open on May 27, 2021. (Applied on Nov. 19, 2019).
30. Awaya A, Kuroiwa Y, Yamashita T. https://geneft.com/article/before-the-dawn-of-the-heyday-of-covid-19-epidemic-in-winter-in-place-of-influenza-summary-of-correlation-between-pollen-exposure-and-kawasaki-disease-onset-and-influenza-epidemic-from-around-1980 published on December 20, 2021. Epidemiology and Public Health Research 2021; 1(2):1-11..
31. Awaya A, Kuroiwa Y. Outbreak of a new coronavirus (SARS-CoV-2) infection and pollen exposure. Arch Community Med Public Health. 2021;7(1):012-016.
32. Awaya A, Kuroiwa Y. A hypothetical discussion of the linkage of airborne pollen exposure to COVID-19 outbreak phenomenon, as well as to development of various intractable diseases and cancers. Epidemiology and Public Health Research. 2021;1(1):1.
33. Akira Awaya, Yoshiyuki Kuroiwa (2021) Remembering the Footsteps of Five Distinguished Ophthalmologists from the Present in the Era of the COVID-19 Pandemic. Medical & Clinical Research 6(7): 630-633.