

Immunology | Research article

Alzheimer's Disease and COVID-19 fatalities linked to the NLRP3 inflammasome overregulation

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Abstract

Objectives: To present a newsworthy hypothesis that illustrates how pollution predisposed long-term living and elderly population to an exacerbation of any preexisting inflammatory conditions, linked to NLRP3 inflammasome overregulation, in individuals with Alzheimer's Disease (AD) and SARS-CoV-2 infections. Also, to discuss the possibility of correlation between AD/SARS-CoV-2 infection and air pollution.

Study Design: The aim of this work is centered on the people living in the two most populated cities in the Canary Islands. Spain, which was motivated by the observed peak of COVID-19 severe patients; and fatalities in Santa Cruz de Tenerife more than in Las Palmas de Gran Canaria over the first COVID wave. It is suggested here that this fact was due to a huge African dust storm in February 2020 during the popular Carnival festivity that was not cancelled following the Government indications for people to stay at home, contrary to other islands that obeyed the objection. Also, in the second wave, the number of cases is much higher in Santa Cruz de Tenerife as well, following the same behavior rules of coexistence for citizens in all the seven major islands. We also analyzed the incidence and mortality due to AD.

Methods: We considered open published data of AD cases per island as well as COVID-19 incidence and mortality [1, 2] and pollution levels sustaining particulate matter and anthropomorphic exhausted gasses [3], linking highly polluted areas to, on one hand, Alzheimer's Disease (AD) and dementia incidence during the past years before 2020 and, on the other hand, a high number of COVID-19 deceases in the eldest patients of the same population in 2020.

Results: In the past years, the city of Santa Cruz de Tenerife presented a higher mortality due to mental and behavior disorders, like, for instance, Alzheimer's disease and dementia, if we compare its numbers with other islands of the same archipelago. Furthermore, in the same metropolitan area COVID-19 is showing higher infection rate and mortality during 2020. Angiotensin-converting enzyme-2 (ACE-2) is overexpressed in AD and Dementia patients (Bostanciklioglu) [4]. As ACE-2 receptors are the entrance pathway for SARS-CoV-2 infection, they should be the factor that links both diseases (Dalan et al.) [5].

Conclusions: An Individual lifetime stay in polluted areas presents a chronic inflammation that adds in an uncontrolled way to the same symptoms of inflammation that ends up killing people because of previous and preinstalled inflamed lungs or other organs, like brain, when they get infected by SARS-CoV-2.

Keywords: Alzheimer's disease; ARDS; COVID-19; Dementia; NLRP3 inflammasome; Platelets; Pollution; SARS-CoV-2.

Background

Inhaled particulate matter suspended in polluted air or anthropogenic pollution gasses such as carbon dioxide (CO₂), nitrogen dioxide (NO₂) and sulfur dioxide (SO₂), expelled and dissolved in the troposphere, runs the nucleotide binding domain and repeated inflammation of leucine-rich protein 3 (NLRP3) inflammasome activation increasing the Interleukin-1 β production and aggravating the inflammation in neurons-microglia and the oligomeric amyloid β (oA β)-induced neuronal injury (Yegambaram et al.) [6]. As very tiny particulate with diameter less than 2.5 microns (PM_{2.5}) and pollution gasses are incorporated to the organism, reactive oxygen species (ROS) level in oA β -stimulated microglia increases. ROS is required for pollution-induced Interleukin-1 β production and NLRP3 inflammasome activation (Macias-Verde et al.) [7].

AD is a leading cause of mortality attributable to genetics in the developed world with 70% risk. The other 30% are hypothesized to include environmental factors and human behavior lifestyle. It is speculated that long term inhalation of these environmental hazards in addition to the bioaccumulation over people's lifetime induced neuroinflammation and neuropathology opening the pathway for developing AD (WHO) [8]. The appearance of the COVID-19 disease revealed that the most common condition of dying between March and April 2020 was Alzheimer's disease and dementia (UK Alzheimer's Society) [9], because of depleted fibrosis lungs after the developed of acute respiratory distress syndrome (ARDS), like it occurs in Wales and England.

AD platelets via a mechanism linked to integrin α IIb β 3 outside-in signaling, expressed at a high level in platelets and their progenitors (Huang et al.) [10], having a high role for mediated pathogenesis of the neuronal disease (Gowert et al.) [11]. It seems that there is an important degree of platelet activation which runs the NLRP3 inflammasome signaling as a possible and underlying mechanism of progression of dementia in AD due to vascular risk factors (Stellos et al.) [12]. Neuron and glial cells are also a target of SARS-CoV-2 infection, which strengthens upon the overexpression of the angiotensin-converting enzyme-2 (ACE-2) receptors in mental and behavior disorder patients (Bostancikliglu) [4]. Dalan et al. [5] describe that SARS-CoV-2 use the same pathway as SARS-CoV in 2002 infecting humans through those same ACE-2 receptors (Conti et al.) [13].

The macrophage NLRP3 inflammasome has also a central importance in the activation of lung inflammation and fibrosis on SARS-CoV-2 infected patients (Lara et al.) [14]. In a recent work published by Macias-Verde et al. [7] based on a wide review about pollution and public health considerations, it is proposed a so-called "Quadrupole Effect Hypothesis" (QEH) between COVID-19 older population and the reactive oxygen species (ROS)

induced by the interaction of the ionizing radiation from radioisotopes sustained in polluted air with human cells, naturally produced as the so-called background radiation or due to human activity, as PM_{2.5} (particulate matter with diameter < 2.5 μ m), PM₁₀ (particulate matter with diameter < 10 μ m), nitrogen dioxide (NO₂), carbon dioxide (CO₂) and sulfur dioxide (SO₂). ROS upregulates the expression of the NLRP3 inflammasome and keep turning on inflammation issues progressively (Macias-Verde et al.) [7].

Methods

Canary Islands Public Government databases [1, 2] provided the necessary information about mental and behavior disorder patient fatality as well of COVID-19 cases in the islands, from where we developed our study.

On the one hand, and to filter the statistical data about health and mental disorders incidence and mortality in this Spanish community, there were selected the following values for the available database parameters included in the graphic user web interface published at *ISTAC (Estadísticas de la Comunidad Autónoma de Canarias. gobiernodecanarias.org)*:

- *Years: All available, from 1999 up to 2018.*
- *Causes of death (reduced list of ICD-10): Mental and behavior disorders.*
- *Sex: Both, male and female.*
- *Age: Complete range up to more than 94 years old.*

On the other hand, we did a qualitative analysis about the air pollution levels in those islands. Courtesy: Day-by-day pollution information given by World's Air Pollution Real-time Air Quality Index webpage [3].

Results

Table 1 as well as Figure 1 shows up the total number of deaths due to AD between 1999 and 2018 in all the islands. Canary Islands are divided into two provinces. On the one hand, Tenerife, La Palma, La Gomera y El Hierro form the province of Santa Cruz de Tenerife, and, on the other hand, Gran Canaria, Lanzarote, and Fuerteventura compose the province of Las Palmas. Although the population is roughly evenly divided between the two, the death cases in the first, mainly in Santa Cruz de Tenerife, capital of the province with the same name, is surprisingly higher than in Las Palmas de Gran Canaria, capital of the province of Las Palmas. Both, Tenerife, and Gran Canaria, have the greater population density if compared with the rest of the shortest islands, and people mainly live in the capitals of both provinces, Santa Cruz de Tenerife, and Las Palmas de Gran Canaria, or in their proximities.

<i>Mental and Behaviour Disorder Mortality. Both sexes (*)</i>								
<i>Islands →</i>	<i>Lanzarote</i>	<i>Fuerteventura</i>	<i>Gran Canaria</i>	<i>Tenerife</i>	<i>La Gomera</i>	<i>La Palma</i>	<i>El Hierro</i>	<i>Tenerife vs Gran Canaria (%)</i>
2018	59	19	246	353	16	27	2	43.5
2017	49	17	198	273	11	28	4	37.9
2016	48	7	188	281	3	30	3	49.5
2015	30	16	188	286	11	25	7	52.1
2014	30	16	157	234	2	28	5	49.0
2013	27	15	191	202	7	33	2	5.8
2012	43	13	199	265	7	24	2	33.2
2011	18	11	178	232	9	47	3	30.3
2010	42	20	184	229	8	25	0	24.5
2009	34	20	173	201	9	26	1	16.2
2008	26	14	154	192	7	22	0	24.7
2007	18	1	102	196	8	25	3	92.2
2006	20	6	112	149	8	30	5	33.0
2005	16	2	132	172	1	20	1	30.3
2004	19	3	131	152	3	13	3	16.0
2003	25	12	136	174	5	15	1	27.9
2002	12	11	112	159	5	25	2	42.0
2001	19	8	106	133	3	25	4	25.5
2000	13	3	148	133	3	23	0	-10.1
1999	14	4	122	132	4	22	2	8.2
<i>2020 COVID-19 cases. Both sexes (**)</i>								
<i>Deceased</i>	9	3	119	162	1	7	1	36.1
<i>Recovered</i>	1128	715	7211	4394	81	169	47	-39.1
<i>At home</i>	65	53	1324	2345	8	9	3	77.1
<i>ICU</i>	0	0	10	25	0	0	0	150.0
<i>In hospital ward</i>	1	4	46	140	2	0	0	204.3

Table 1. (*) Alzheimer's Disease death cases in the Canary Islands. Instituto Canario de Estadística (ISTAC), Instituto Nacional de Estadística (INE) y Consejería de Sanidad. Gobierno de Canarias. Copyright: 2020. www.gobiernodecanarias.org/istac.consultas.istac@gobiernodecanarias.org

(**) PublicHealth. Gobierno de Canarias. (<https://www3.gobiernodecanarias.org/sanidad/scs/contenidoGenerico.jsp?idDocument=83670f95-f738-11ea-8b38-0997195c2925&idCarpeta=e01092c2-7d66-11ea-871d-cb574c2473a4>).

Mental disorders decrease comparison statistics reveals the same pattern in the percentage difference between the two capitals in the last four years in both islands, from 2014 up to 2018 (Table 1), converging with the figures of COVID-19 deaths in 2020, around 40% greater in Santa Cruz de Tenerife in both cases. The number of recoveries in Las Palmas de Gran Canaria presents the same better percentage versus the situation in Santa Cruz de Tenerife. As it happens in other countries, it is found that there is a relation between deaths due to AD with COVID-19 fatalities.

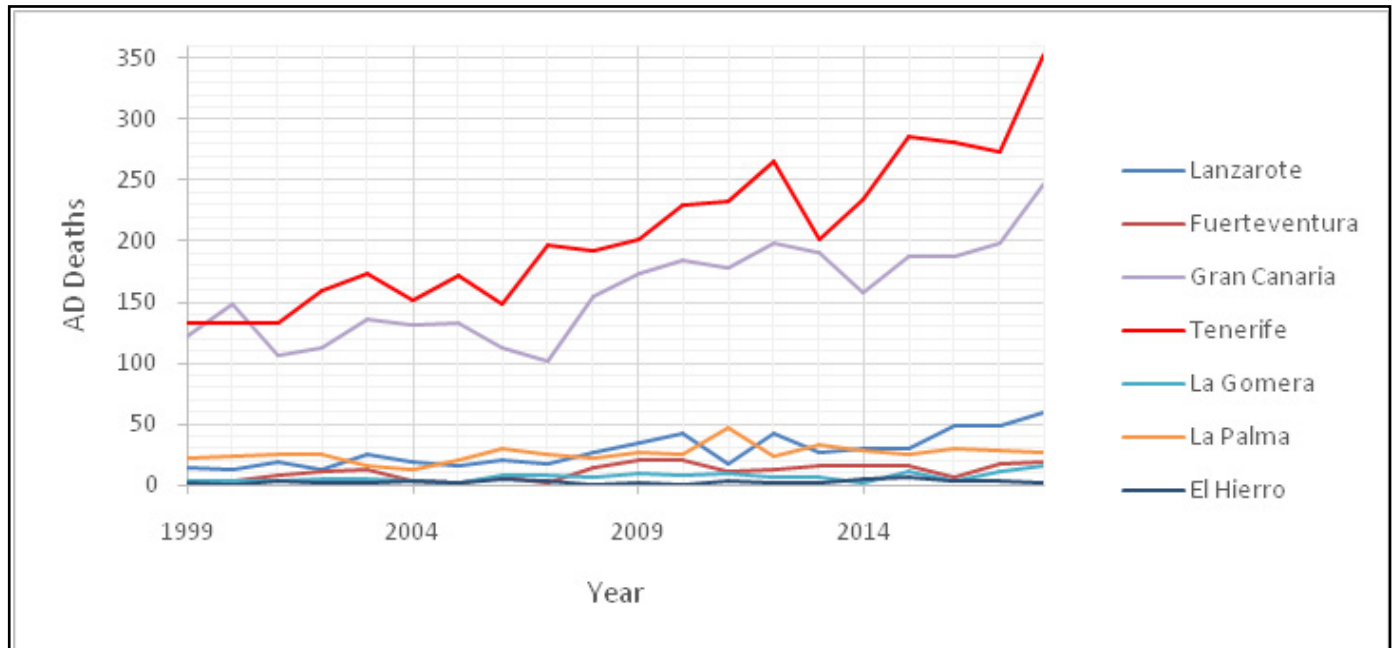


Figure 1. Alzheimer's Disease death cases in the Canary Islands as shown in Table 1. Instituto Canario de Estadística (ISTAC), Instituto Nacional de Estadística (INE) y Consejería de Sanidad. Gobierno de Canarias. Copyright: 2020.

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Discussion

QEH points out that sustained polluted environments which includes anthropogenic $PM_{2.5}$ or exhausted gasses which are continuously interchanging some of its non-radioactive elements like carbon or nitrogen with radiocarbon or radionitrogen, which are unstable emitting ionizing radiation nuclei constantly created naturally in the atmosphere, are a source of continuous production organ inflammation diseases due to inhalation of polluted air (Macias-Verde et al.) [7]. Other compounds, like SO_2 , can cause acid rains giving major mobility to the progenies of the natural radioactive series of uranium, thorium and actinium elements and facilitating their absorption by plants becoming more hazardous to humans.

Macias-Verde et al. [7] relate outdoor and indoor natural radioactivity in particulate matter with organ inflammation as well. Probably, this could explain the huge incidence of COVID-19 severity in countries with the highest background radiation over the planet, such as Brazil, India, or Iran.

Although the case of the Spanish Archipelago of the Canary Islands, in the Northern coast of Africa, could present an example of AD developed due to environmental hazards dissolved in air, its relationship with radioactivity should

be studied in greater detail. Despite the reasons are not specifically known, there are several facts that could explain why the city of Santa Cruz de Tenerife, in the island of Tenerife, has a major incidence of AD fatality cases and a worst evolution or severity of COVID-19 patients. It could be due to several facts:

- A petrol refinery was working beside the greater metropolitan area between 1930 and 2015 throwing dirty fumes downtown.
- The presence of tons of carbon dioxide pushed out daily to the troposphere by Volcano Teide, in the center of the island (INVOLCAN) [15], possibly converted in unstable radiocarbon dioxide (Macias-Verde et al.) [7].
- Santa Cruz de Tenerife, the most populated site in Tenerife, and its capital, is located inside the Massif of Anaga and the so-called Trade winds do not quickly wash out the air [16, 17].
- Exhausted gasses from vehicles suffers the same stationary fate due to the blocked winds by the Massif and could be as well converted in radioactive molecules. It is known that some radioactive nitrogen is produced in the atmosphere when high energy cosmic radiation from the sun hits the Earth. In other countries, nitric and nitrous acids or their salts have been observed in the blood and urine after exposure to nitrogen dioxide (WHO) [18].

An initial qualitative data examination along the Canary Islands via World's Air Pollution Real-time Air Quality

Index webpage [3], shows up worst air conditions along the year in Santa Cruz de Tenerife. As population in Tenerife is living mainly in Santa Cruz de Tenerife and those people located in Gran Canaria are living mainly in Las Palmas de Gran Canaria, we assume Tenerife and Gran Canaria as if they had all the people living in the capitals. Anyway, in those islands all the cities although they are not together, they are almost one after each other in a continuous line due to the short surface of that Archipelago.

Conclusion

Dalan et al. [4] found out that SARS-COV-2 use the same pathway as SARS-CoV, infecting humans through the angiotensin-converting enzyme-2 (ACE-2) receptor. PM_{2.5} long-term exposure leads to alveolar angiotensin-converting enzyme-2 (ACE-2) receptor overexpression (Frontera et al.) [19], that may increase viral load in patients exposed to pollutants in turn depleting ACE-2 receptors and impairing host defenses (Frontera et al.) [19]. Neuron and glial cells are also a potential target of COVID-19 due to the overexpression of ACE-2 receptors in dementia or Alzheimer's Disease patients (Bostanciklioglu et al.) [5].

Since both conditions seems to have the same ending, the evolution of patients from this new disease, that emerged at the end of 2019, has shed light establishing a possible cause for a relation between AD fatalities suggesting that the effects of radioisotopes in PM_{2.5} and indoor and/or outdoor natural background radiation under AD context were possibly mediated by NLRP3 inflammasome activation, which is triggered by reactive oxygen species possibly started by ionizing radiation between others and uncertain reasons yet. It seems that there are possible reasons to point out common environmental factors that promotes prior chronic inflammatory processes linked to an upregulated action of the NLRP3 inflammasome that might be leading to a high severe side effects of several organ inflammation.

We postulate, like many other studies in the scientific literature reviewed by Macias-Verde et al. [7], that pollution predisposed long-term living and elderly population of that highly polluted areas to have a predisposed inflamed organ that leads to uncontrolled innate immune system responses. Given the great differences and considering that health care is the same in all the archipelago of the Canary Islands, we must look more deeply at the reasons for such abnormality. Finally, not only a qualitative analysis but a statistical and more detail study including air pollution concentrations should be done in the extremely near future.

Patient Consent statement

There are no patients involved in this work so there is no need for a patient consent statement.

Conflicts of Interest statement

Authors declare no conflicts of interest.

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Abbreviations

- i. ACE-2: Angiotensin-converting enzyme-2.
- ii. AD: Alzheimer's disease
- iii. ARDS: Acute respiratory distress syndrome.
- iv. CO: Carbon monoxide.
- v. CO₂: Carbon dioxide.
- vi. COVID-19: Coronavirus disease-2019.
- vii. ICD-10: International Statistical Classification of Diseases and Related Health Problems-10.
- viii. NLRP3: Nucleotide binding domain and repeated inflammation of leucine-rich protein 3.
- ix. NO₂: Nitrogen dioxide.
- x. α A β : Oligomeric amyloid beta.
- xi. ORF: Open reading frame.
- xii. PAMP: Pathogen-associated molecular pattern.
- xiii. PM₁₀: Particulate matter with diameter <10 μ m.
- xiv. PM_{2.5}: Particulate matter with diameter < 2.5 μ m.
- xv. ROS: Reactive oxygen species.
- xvi. SARS-COV-2: Severe acute respiratory syndrome coronavirus-2.
- xvii. SO₂: Sulfur dioxide.
- xviii. WHO: World Health Organization
- xix. QEH: Quadrupole Effect Hypothesis

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