Environmental Research 166 (2018) 348–362

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Alzheimer's disease and alpha-synuclein pathology in the olfactory bulbs of infants, children, teens and adults ≤ 40 years in Metropolitan Mexico City. APOE4 carriers at higher risk of suicide accelerate their olfactory bulb pathology

Lilian Calderón-Garcidueñas[a,b,*], Angélica González-Maciel[c], Rafael Reynoso-Robles[c], Randy J. Kulesza[d], Partha S. Mukherjee[e], Ricardo Torres-Jardón[f], Topi Rönkkö[g], Richard L. Doty[h]

[a] The University of Montana, Missoula, MT, 59812, USA
[b] Universidad del Valle de México, 14370, Mexico
[c] Instituto Nacional de Pediatría, Mexico City, 04530, Mexico
[d] Auditory Research Center, Lake Erie College of Osteopathic Medicine, Erie, PA 16509, USA
[e] Mathematics Department, Boise State University, Boise, ID 83725, USA
[f] Centro de Ciencias de la Atmósfera, Universidad Nacional Autónoma de México, 04310, Mexico
[g] Aerosol Physics, Faculty of Natural Sciences, Tampere University of Technology, FI-33101 Tampere, Finland
[h] Smell and Taste Center, Department of Otorhinolaryngology: Head and Neck Surgery, Perelman School of Medicine, University of Pennsylvania, 19104, USA

ARTICLE INFO

Keywords:
Alzheimer
Alpha synuclein
Alpha-synucleinopathies
Amyloid plaques
Air pollution
APOE4
Children
Corpora amylacea
Combustion-derived nanoparticles CDNPs
Hyperphosphorylated tau
Mexico City
Nanocluster aerosol particles
Olfactory bulb
Parkinson
$PM_{2.5}$
Suicide
Tauopathies
Young adults

ABSTRACT

There is growing evidence that air pollution is a risk factor for a number of neurodegenerative diseases, most notably Alzheimer's (AD) and Parkinson's (PD). It is generally assumed that the pathology of these diseases arises only later in life and commonly begins within olfactory eloquent pathways prior to the onset of the classical clinical symptoms. The present study demonstrates that chronic exposure to high levels of air pollution results in AD- and PD-related pathology within the olfactory bulbs of children and relatively young adults ages 11 months to 40 years. The olfactory bulbs (OBs) of 179 residents of highly polluted Metropolitan Mexico City (MMC) were evaluated for AD- and alpha-synuclein-related pathology. Even in toddlers, hyperphosphorylated tau (hTau) and Lewy neurites (LN) were identified in the OBs. By the second decade, 84% of the bulbs exhibited hTau (48/57), 68% LNs and vascular amyloid (39/57) and 36% (21/57) diffuse amyloid plaques. OB active endothelial phagocytosis of red blood cell fragments containing combustion-derived nanoparticles (CDNPs) and the neurovascular unit damage were associated with myelinated and unmyelinated axonal damage. OB hTau neurites were associated mostly with pretangle stages 1a and 1b in subjects ≤ 20 years of age, strongly suggesting olfactory deficits could potentially be an early guide of AD pretangle subcortical and cortical hTau. APOE4 versus APOE3 carriers were 6–13 times more likely to exhibit OB vascular amyloid, neuronal amyloid accumulation, alpha-synuclein aggregates, hTau neurofibrillary tangles, and neurites. Remarkably, APOE4 carriers were 4.57 times more likely than non-carriers to die by suicide. The present findings, along with previous data that over a third of clinically healthy MMC teens and young adults exhibit low scores on an odor identification test, support the concept that olfactory testing may aid in identifying young people at high risk for neurodegenerative diseases. Moreover, results strongly support early neuroprotective interventions in fine particulate matter ($PM_{2.5}$) and CDNP's exposed individuals ≤ 20 years of age, and the critical need for air pollution control.

1. Introduction

Urban polluted environments and occupational exposures with ubiquitous high concentrations of ultrafine particles (UFP, diameter < 100 nm) (Zhu et al., 2002; Pirjola et al., 2016), nanoparticles (NP, diameter < 100 nm), and the recently discovered nanocluster aerosol particles (NCA, diameter < 3.0 nm) (Rönkkö et al., 2017) emitted by road transportation are of great concern for the nervous system due to their high potential to penetrate biological barriers, including vascular endothelium, alveolar-capillary, olfactory, nasal,

* Corresponding author at: University of Montana, 32 Campus Drive, 287 Skaggs Building, Missoula, MT 59812, USA.
E-mail address: lilian.calderon-garciduenas@umontana.edu (L. Calderón-Garcidueñas).

https://doi.org/10.1016/j.envres.2018.06.027
Received 7 May 2018; Received in revised form 12 June 2018; Accepted 12 June 2018
0013-9351/ © 2018 Elsevier Inc. All rights reserved.

gastrointestinal, blood-brain-barrier (BBB) and blood-CSF barrier (Maher et al., 2016; González-Maciel et al., 2017; Calderón-Garcidueñas et al., 2018). Combustion aerosol particle sources, i.e., vehicles powered with internal combustion engines and combustion-based production of heat and power, are frequently situated closed to people increasing their relative importance in respect of human exposures to particulate matter (PM). Combustion-originated particles are composed of elemental carbon, organic and sulfuric compounds and metals (Enroth et al., 2016; Mylläri et al., 2017; Rönkkö et al., 2014) found in fuels, lubricant oils and engine wear. Iron and associated transition metals of NPs are highly oxidative and strongly magnetic (Maher et al., 2016). The entire range of very small particles gain entry to the brain in significant amounts in children, and young adult Metropolitan Mexico City (MMC) residents and are known to cause severe damage to critical cellular organelles in the central nervous system (CNS) (Calderón-Garcidueñas et al., 2016a, 2017; González-Maciel et al., 2017).

Exposure to air pollutants appear to play a major role in the development and/or acceleration of Alzheimer's disease (AD) (Calderón-Garcidueñas et al., 2002, 2008a, 2008b; González-Maciel et al., 2017; Jung et al., 2015; Maher et al., 2016; Chen et al., 2017; Marabotti et al., 2017). MMC residents who live under high levels of air pollution show an early brain imbalance in genes involved in oxidative stress, inflammation, and innate and adaptive immune responses (Calderón-Garcidueñas et al., 2012). Dysregulated neuroinflammation, diffuse brain neurovascular unit damage, and the accumulation of misfolded proteins associated with the early stages of both AD and Parkinson's disease (PD) are seen in MMC residents, but not in individuals coming from regions of low air pollution (Calderón-Garcidueñas et al., 2003, 2007b, 2008b, 2010, 2011, 2012, 2016a, 2016b, 2017). Olfactory dysfunction is a hallmark of these disorders, occurring long before the onset of their clinical phenotypic manifestations (Doty, 2012, 2017). Because of this fact, and evidence that nanoparticles and other components of air pollution can enter into the nose, bypass the blood brain barrier, and penetrate the brain via the olfactory receptor cells and perineural spaces, the olfactory bulbs (OBs) have become a primary focus for understanding the relationship between air pollution and neurodegenerative disease pathology (Doty, 2008). The OBs clearly participate in the brisk neuroinflammatory process related to exposures to polluted air where particulate matter and metals are key components, along with endotoxins and CDNPs (Bravo-Alvarez and Torres-Jardón, 2002; Vega et al., 2010; Molina et al., 2010; Aiken et al., 2009; Marr et al., 2006; Querol et al., 2008; Calderón-Garcidueñas et al., 2013).

We have previously described the association between olfactory bulb apurinic/apyrimidinic (AP) lesion sites in genomic DNA and the presence of metals like Ni and V (from industrial environmental sources). A pathologic gradient was identified (olfactory mucosa > olfactory bulb > frontal cortex) which included significant OB neuroinflammation and upregulation of IL1β and COX2 in MMC residents (Calderón-Garcidueñas et al., 2003, 2013). The clinical counterpart was seen in MMC children (13.4 ± 4.8 years, 28 APOE 3 and 22 APOE 4), where the failure of APOE4 children to identify the soap odor in the University of Pennsylvania Smell Identification Test (UPSIT) was correlated with a higher mI/Cr ratio in the left hippocampus (Calderón-Garcidueñas et al., 2015). Earlier, we demonstrated OB pathology in a cohort of 35 MMC vs 9 control subjects ages 20.8 ± 8.5 years assessed by light and electron microscopy (Calderón-Garcidueñas et al., 2010). MMC residents showed, with no exceptions, OB vascular changes, neuronal accumulation of particles, and/or immunoreactivity (IR) to beta amyloid and/or alpha-synuclein in neurons, glial cells, and/or blood vessels. CDNPs were documented in the endothelial cytoplasm and basement membranes of the OBs. In contrast to Mexico City olfactory bulb extensive pathology, the OBs from clean air control residents were unremarkable (Calderón-Garcidueñas et al., 2010). In the same work we also described the results of the UPSIT administration to 62 MMC v 25 controls age 21.2 ± 2.7 years. Olfaction deficits were present in 35.5% MMC and 12% of controls (Calderón-Garcidueñas et al., 2010). Of considerable interest was the observation that APOE 4 carriers failed 2.4 ± 0.54 items in the 10-item smell identification scale from the UPSIT related to Alzheimer's disease, while APOE 2/3 and 3/3 subjects failed 1.36 ± 0.16 items, a highly significant result p = 0.01 (Calderón-Garcidueñas et al., 2010).

In this study we documented, using immunohistochemistry, the early stages of AD- and α-synuclein-related olfactory bulb pathology in young persons living in highly polluted regions of MMC. We employed electron microscopy to document vascular pathology and to identify and measure the sizes of combustion-derived nanoparticles and the associated organelle pathology within the bulbs. Our laboratory is particularly interested in the progression of olfactory bulb pathology with age and cumulative exposures to fine particulate matter ($PM_{2.5}$) above the USEPA standard (primary: 12 μg/m^3, annual mean averaged over 3 years). Identifying key air pollutants, composition and sizes of nanoparticles, and other factors that impact early neural risk within the olfactory system and its interrelated CNS structures has the potential to allow for modifying the course of AD and PD during their genesis early in life.

2. Methods

2.1. Study design and samples

One hundred and seventy-nine consecutive autopsies with sudden causes of death that it did not involve the brain were selected for this study. MMC subjects ages 11 months to 40 years were clinically healthy prior to their sudden demise and were included in this study if:

(a). Sections of olfactory bulb contained the anterior olfactory nucleus, granular, plexiform and glomerular layers and olfactory tract white matter, (b). Gross examination of the brain was unremarkable, and (c). Macro and microscopic examination of extra-neural key organs was unremarkable. Examination of autopsy materials was approved by the Forensic Institute in Mexico City. Autopsies were performed 4.2 ± 1.3 h after death between 2004 and 2008 and samples were collected by 4 trained researchers, weekdays, weekends and holidays during the 5 year study period. Brains were examined macroscopically, sections were selected for light and electron microscopy, and frozen tissues collected. The general characteristics of the study population, including their cause of death are seen in Table 1 (Suppl). An average of 46 ± 11 olfactory bulb slides were examined per case. Paraffin embedded tissue was sectioned at a thickness of 7 μm and stained with hematoxylin and eosin (HE). Immunohistochemistry (IHC) was performed on serial sections as previously described (Calderón-Garcidueñas et al., 2008b). Antibodies included: β amyloid 17–24, 4G8 (Covance, Emeryville, CA 1: 1500), PHF-tau8 phosphorylated at Ser199–202-Thr205 (Innogenetics, Belgium, AT-8 1:1000), and α-synuclein phosphorylated at Ser-129, LB509 (In Vitrogen, Carlsbad, CA 1:1000). A number of brain tissues from all cases included in this work were previously blindly investigated for purposes of AD (Calderón-Garcidueñas et al., 2018). Olfactory bulbs were examined for AD and alpha-synucleinopathies hallmarks (Kovacs et al., 1999, 2001; Thal et al., 2002; Tsuboi et al., 2003; Braak et al., 2003, 2011a, 2011b, 2015, 2017; Del Tredici et al., 2002; Del Tredici and Braak, 2016; Attems et al., 2005, 2006, 2014; McKeith et al., 2005; Beach et al., 2009; Rüb et al., 2016). Tau pathology was scored using separate semiquantitative scores for neuropil threads (NTs) and neurofibrillary tangles (NFTs): 0 = absent, 0.5 = very mild (only single lesions), 1 = mild, 2 = moderate, and 3 = severe (Attems et al., 2005, 2006, 2014). The β- amyloid scoring was semiquantitative: 0 = absent, 1 = mild, few diffuse Aβ positive areas, no plaques, 2 = moderate, ≤ 3 plaques per high power field (HPF) x 200, and 3 = severe, 4 or more plaques HPF x 200 (Attems et al., 2014). Intracellular Aβ was scored 0 = absent and 1 = positive; vascular β- amyloid 0, 1,2 and 3 (severe). Alpha-synuclein was scored

Download English Version:

https://daneshyari.com/en/article/8868829

Download Persian Version:

https://daneshyari.com/article/8868829

Daneshyari.com