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White Matter Hyperintensities, Systemic Inflammation, Brain Growth, and Cognitive Functions in Children Exposed to Air Pollution

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Abstract. Air pollution exposures are linked to neuroinflammation and neuropathology in young urbanites. Forty percent of exposed children and young adults exhibit frontal tau hyperphosphorylation and 51% have amyloid-β diffuse plaques compared to 0% in low pollution controls. In older adults, white matter hyperintensities (WMH) are associated with cognitive deficits while inflammatory markers correlate with greater atrophy than expected for age. We investigated patterns of WMH, magnetic resonance imaging (MRI) volume growth, blood inflammatory mediators, and cognition in matched children from two urban cohorts: one severely and one minimally exposed to air pollution. Baseline and one year follow-up measurements of cognitive abilities, brain MRI volumes, and blood were collected in 20 Mexico City (MC) children (10 with WMH^+, and 10 without WMH^-) and 10 matched controls (WMH^-). MC WMH^- children display the profile of classical pro-inflammatory defensive responses: high interleukin 12, production of powerful pro-inflammatory cytokines, and low concentrations of key cytokines and chemokines associated with neuroprotection. MC WMH^+ children exhibit a response involved in resolution of inflammation, immunoregulation, and tissue remodeling. The MC WMH^+ group responded to the air pollution-associated brain volumetric alterations with white and grey matter volume increases in temporal, parietal, and frontal regions and better cognitive performance compared to MC WMH^-. We conclude that complex modulation of cytokines and chemokines influences children's central nervous system structural and volumetric responses and cognitive correlates resulting from environmental pollution exposures.

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Identification of biomarkers associating systemic inflammation to brain growth is critical for detecting children at higher risk for cognitive deficits and neurodegeneration, thereby warranting early implementation of neuroprotective measures.

Keywords: Air pollution, Alzheimer's disease risk, biomarkers, chemokines, children, cognition, cytokines, fine particulate matter, MRI volumes, systemic inflammation, white matter hyperintensities

Supplementary data available online: http://www.j-alz.com/issues/31/vol31-1.html#supplementarydata04

INTRODUCTION

Increasing evidence links neuroinflammation to neurodegenerative disease, particularly Alzheimer's disease (AD) [1]. Air pollution exposures have been linked to neuroinflammation and neuropathology in young urbanites: 40% of highly exposed children and young adults exhibit frontal tau hyperphosphorylation with pre-tangle material and 51% have amyloid-β diffuse plaques compared with 0% in low pollution controls [2]. The presence of abnormally phosphorylated tau protein in nerve cells or in portions of their cellular processes has been reported by Braak and Del Tredeci [3] in subjects ages 4 to 29, supporting the idea that AD-related pathology can start in young adulthood and even earlier in childhood. In particular, it has also been reported that 56% of a sample of clinically healthy Mexico City (MC) children exhibited magnetic resonance imaging (MRI) prefrontal white matter hyperintensities (WMH), compared to 7.6% in age-matched children from a low polluted area, with significant selective impairment in attention, short term memory, and learning ability without known risk factors for cognitive and neurological deficits [4].

Systemic inflammation and increased concentrations of potent vasoconstrictors (i.e., endothelin-1) are key features of exposure in MC children. They correlate with cumulative exposures to fine particulate matter and outdoor exposure hours, and are a reflection of the sustained chronic inflammation of the upper and lower respiratory tracts and endothelial dysfunction [5–7]. Air quality in Mexico City stands among the worst in the world [8]. Children are exposed all year long to a significant burden of air pollutants, including concentrations above the current US standards for ozone, and fine particulate matter<2.5 μm in diameter ($PM_{2.5}$). Exposures of today's children are truly lifelong and include the exposures of their mothers during pregnancy.

WMH are associated with clinical symptoms related to disruption of fiber tracts, cognitive impairment risk, cerebral ischemia, neurodegeneration, cardiovascular, and metabolic diseases [9–17]. In elderly adults, WMH partially identify underlying white matter pathology and are associated with lesions developing in surrounding tissues [18], while the target cognitive domain affected is executive function [14]. WMH are likely the tip of the iceberg in exposed children [19] and may be associated with widespread white matter changes, the novel concept of WMH penumbra [20]. Disruption of fiber tracts could result in cortical cholinergic and monoaminergic deafferentiation and impact attention, emotion, and goal-directed behavior [11]. Thus the characterization of WMH in young urbanites matters because it may shed light into the etiopathogenesis of a well-characterized risk factor for neurodegeneration, vascular cognitive disorders, and disability [18–21].

In two recent studies, we have shown WMH and brain volumetric changes associated with cognitive deficits in highly exposed children [4, 19]. Intriguingly, our studies suggested that in some MC children, WMH could coexist with altered growth in key brain areas and with increased signs of systemic inflammation, but also with better than expected cognitive outcomes. These observations raise the question: what do WMH represent in highly exposed children—could they signal and/or be associated with a temporary reparative response against neuroinflammation linked with severe air pollution exposure?

Given that the relationship between inflammatory mediators and children's central nervous system (CNS) structural and volumetric responses and cognitive correlates resulting from severe air pollution exposure may be of critical importance for the understanding the etiopathogenesis of key structural surrogate markers of small vessel disease, vascular cognitive disorders, and neurodegeneration (i.e., AD risk), the goal of this follow-up study was to investigate patterns of MRI volume growth, target inflammatory mediators (TNF-α, MCP-1, IL12, CCL22, and G-CSF), and cognitive profiles in matched samples carefully selected from two previously studied cohorts of MC and control children.

Our guiding framework is that the etiopathogenesis of WHM, a well-characterized risk factor for neurodegeneration, vascular cognitive disorders, and disability [18–21], may be explained in terms of the

developmental relationships between brain growth, neuroinflammation, and cognitive outcomes. Accordingly, we hypothesized that if WMH indeed reflect temporary repair responses, WMH should coexist with regional brain overgrowth (as integrated in the compensatory scheme) and a distinct pattern of inflammatory mediators in highly exposed MC children, compared to MC children with no WMH or control children. Furthermore, as a byproduct of the coexistence between WMH and specific gray and white matter volume increases, MC children with WMH may show higher cognitive performance than their MC counterparts without WMH. Finally, to establish how the brain volume growth could be related to systemic inflammation and neuroinflammation, we examined whether the expression of selected key cytokines and chemokines showed distinctive expression patterns across the groups consistent with the MRI patterns.

PROCEDURES

Study areas

The selected areas were Southwest Mexico City (SWMC), a severely air polluted region within a megacity, and Polotitlán in the state of Mexico, a clean environment with concentrations of the six criteria air pollutants (ozone, particulate matter, sulfur dioxide, nitrogen oxides, carbon monoxide, and lead) below current US standards [4, 19].

Participants

This research was approved by the research ethics committee of the Instituto Nacional de Pediatría, Mexico City, Mexico, and The Center for Structural and Functional Neurosciences, The University of Montana, Missoula, USA. The committee's recommendations were thoroughly followed. Children gave active assent and their parents gave written informed consent to participation. This work includes data from 20 MC children (10 with WMH (WMH^+), mean age = 7.28 y, SD = 0.47, 6 female; and 10 without WMH (WMH^-), mean age = 7.04 y, SD = 0.51, 4 female) and 10 controls (CTL; mean age = 7.06 y, SD = 0.45, 6 female) carefully selected to represent comparable populations recruited for a larger longitudinal cohort research program. Clinical inclusion criteria for all children were negative smoking history and environmental tobacco exposure, lifelong residency in MC or control city, residency within 5 miles of the city monitoring stations, full term birth, and unremarkable clinical histories, including no hearing or visual impairments. Children were matched by age and socioeconomic status and had similar body mass index (BMI) (mean = 16.9, SD = 2.4) or height (mean = 1.2 m, SD = 0.3). In addition to the general inclusion criteria, the specific criterion for the selection of half of the MC sample was detection of WMH in their MRI brain scans (see below).

Pediatric examination

Children were followed for two years, had initial complete clinical histories and physical examinations, and underwent two annual pediatrician check-up visits. All included children were clinically healthy and similarly actively engaged in outdoor activities (range: 3.2–4.9 h daily).

Peripheral blood analysis

Blood samples were collected for a complete blood count only in 2008 with differential and custom-made human multianalyte Elisa cytokine arrays, including: tumor necrosis factor alpha (TNF-α), granulocyte monocyte chemoatractant protein-1 (MCP-1), chemokine CC motif ligand 22 (CCL22), granulocyte colony-stimulating factor (G-CSF), and interleukin 12 (IL-12 p40) (Multi-Analyte ELISArray Kits, SABiosciences, Frederick, MD, USA).

Cognitive profiles of the groups

Cognitive profiles of the groups were measured using the subscales of the Wechsler Intelligence Scale for Children-Revised (WISC-R) on baseline (2007) and follow-up year (2008). Preliminary comparisons revealed no reliable between-groups IQ differences [19]. However, both WMH^- and WMH^+ groups showed consistent and progressive, albeit selective, deficits in Vocabulary and Digit Span subscales, relative to CTL. There were no consistent differences between WMH^- and WMH^+ over the two years, except that WMH^+ children had significantly higher scores than WMH^- counterparts in the Picture Completion subscale at follow-up, whereas the lead was reversed for the Arithmetic subscale in both years.

Brain magnetic resonance imaging (MRI)

All 30 children underwent a brain MRI in the summer of the baseline and follow-up year. The 3D MRI for all subjects was acquired on a 1.5 Tesla 5T Signa Excite HD MR (General Electric, Milwaukee WI,

USA) with an 8 Channel Brain Array. The goal of the selected acquisition protocol was to allow a) for brain structure assessment via global and regional brain volumes, and b) for WMH visual assessment. WMH were defined as hyperintense focal images observed in two different sequences: T2 and T2 weighted with fluid-attenuated inversion recovery (FLAIR). High-resolution T1 weighted anatomical images (3D SPGR, voxel dimensions $0.9375 \times 0.9375 \times 1.5$ mm, 256×256 voxels, 124 slices, axial, 15 min) were acquired, as well as T2 weighted images using a 2D multi-slice dual fast spin echo sequence (FSE, voxel dimensions $0.9375 \times 0.9375 \times 2$ mm, axial, 10 min) and fluid attenuated inversion recovery images [19]. All sequences covered the entire surface of the brain. Measurements of sub-cortical bilateral volumes including hippocampus, caudate, putamen, globus pallidus, and amygdala were included. The total scanning time was approximately 45 min. For image processing, every individual structural MRI dataset, probabilistic tissue segmentations of white matter, gray matter, and cerebrospinal fluid were computed in automatic fashion by our atlas-based tissue classification [22–24]. Skull stripping, intensity inhomogeneity correction [23], and intensity calibration were additionally performed in this step. In the next step, a prior brain atlas, derived as an unbiased, symmetric average image in as separate study, is deformed to match each MRI image via non-linear high-dimensional fluid deformation [25]. The atlas's structural probabilistic region of interest (ROI) definition of the lobar parcellations is propagated to each subject's image using the computed deformation field [26]. Propagated ROIs and parcellations were reviewed for accuracy and edited only if they deviated significantly from critical, well-defined boundaries. The parcellation for each subject was then combined with that subject's tissue classification to obtain white matter, gray matter, and cerebrospinal fluid volumes for each lobe and region. The corresponding volumetric measurements for ROIs and parcellations were automatically computed. Both whole ROI and parcellation computation methodology has been validated and evaluated for stability. Repeatability studies show coefficients of variance less than 1.5% for all measurements.

Data analysis

For both WISC-R and MRI data, mixed-model ANOVAs with full factorial design were preliminarily run; for MRI: Volume [white versus grey matter] X Year [2007 versus 2008] X Group [MC WMH^+, MC WMH^-, and CTL] X Hemisphere [Right versus left] X Brain Region [occipital cortex, temporal cortex, subcortical structures, frontal cortex, frontal cingulated gyrus, parietal cortex, parietal cingulated gyrus, cerebellum, corpus callosum, prefrontal cortex, and insula]; for WISC-R: WISC-R Measure [Information, Similarities, Arithmetic, Vocabulary, Comprehension, Digit Span, Picture Arrangement, Block Design, Object Assembly, Coding, and Mazes] X Year [2007 versus 2008] X Group [MC WMH^+, MC WMH^-, and CTL]. Based on the latter, a more in-depth analysis was then performed using focused contrasts on the data collapsed over the two years, for the WISC-R data, and collapsed over the two years, hemispheres and volume, for the MRI data.

The polynomial orthogonal contrasts specifically tested quadratic models testing the alternative hypothesis: $WMH^+ = CTL > WMH^-$ (rejecting the null hypothesis with $p < 0.05$, two-tailed).

The inflammatory markers data were only analyzed through equivalent *t*-test contrasts testing the aforementioned quadratic models.

RESULTS

MRI data

The preliminary analysis (see supplementary Table 1; available online: http://www.j-alz.com/issues/31/vol31-1.html#supplementarydata04) showed various main effects but no interactions involving the group differences relevant to the testing of our hypothesis, except crucially the interaction Group X Brain Region, showing volume growth differed across groups in specific brain regions; this did not change by year or hemisphere. The follow-up quadratic contrasts (see Table 1) confirmed that in the MC WMH^+ group, brain volume (both grey and white matter) grew significantly more than their MC WMH^- counterpart in temporal, parietal, and frontal cortical regions. However, the MC WMH^+ group and the CTL did not differ, and there were no other significant growth differences across regions among groups.

Cognitive data

While the preliminary analysis showed significant variations across the WISC-R subscale mean scores ($F(6, 158) = 5.046$, $MSE = 59.06$, $p < 0.001$), there were no other significant effects, particularly, no significant changes from baseline to follow-up year. Thus, Table 2 reports the adjusted means for

Table 1
Means of MRI regional brain volume bilateral measurements in children from Mexico City with white matter hyperintensities (MC WMH^+) and without (MC WMH^-) and in matched control children (CTL) from Polotitlán exposed to air pollution concentrations below the US standards

Brain region	Group			$MSE_{contrast}$	$F_{contrast}$
	MC WMH$^+$	*MC WMH*$^-$	*CTL*		
Occipital cortex	23774.65	22653.47	22785.46	1253.16	0.28
Temporal cortex	54739.14	50771.49	52049.61	5245.76	4.85*
Subcortical areas	22152.94	21390.21	21837.78	1210.30	0.26
Frontal cortex	51761.52	48626.94	50545.01	5052.66	4.50*
Cerebellum	30025.87	29817.55	31496.29	1887.06	0.63
Insula	5132.37	4684.35	4916.51	680.17	0.08
Parietal cingulated	2318.87	2219.90	2299.23	178.30	0.01
Parietal cortex	74211.66	68915.15	70484.10	6865.46	8.30**
Corpus callosum	3639.53	3407.63	3514.66	338.94	0.02
Frontal cingulated	3857.42	3712.42	3850.78	283.36	0.01
Prefrontal cortex	35307.28	33633.39	34860.57	2901.07	1.48

Note. The values represent means of total brain volume (i.e., white and grey matter volumes) measurements in cubic millimeters; the data was collapsed over baseline and follow-up years, hemisphere and volume (gray and white matter). Contrast model weight values were, +1, −2, +1, respectively. $MSE_{within} = 9461081.38$. *$p < 0.05$; **$p < 0.01$.

Table 2
Adjusted means for the WISC-R measures collapsed over baseline and follow-up year estimated from general linear model with WML status, Mexico City status versus Control, and gender as covariates

WISC measure	Group			$MSE_{contrast}$	$F_{contrast}$
	MC WMH$^+$	*MC WMH*$^-$	*CTL*		
Information	8.75	9.05	9.55	0.20	0.04
Similarities	10.10	10.05	10.10	0.10	0.01
Arithmetic	11.50	10.05	10.55	1.95	3.42*
Vocabulary	10.35	9.30	9.10	0.85	0.65
Comprehension	10.65	10.45	9.60	0.65	0.38
Digit span	8.80	7.20	8.20	2.60	6.08***
Picture comprehension	11.05	10.20	9.90	0.55	0.27
Picture arrangement	10.20	10.20	8.25	1.95	3.42*
Block design	10.70	9.65	9.25	0.65	0.38
Object assembly	10.10	9.15	10.45	2.25	4.55**
Coding	11.00	10.10	10.80	1.60	2.30
Mazes	10.75	8.85	9.20	2.25	4.55**

Note. Contrast model weight values were, +1, −2, +1, respectively. $MSE_{within} = 5.56$. The data was collapsed over baseline and follow-up years. *$p < 0.05$; **$p < 0.025$; ***$p < 0.001$.

the WISC-R measures collapsed over baseline and follow-up year estimated from general linear model with WML status, Mexico City status versus Control, and gender as covariates. The trend in the WISC-R data mirrored the pattern in the MRI data for Arithmetic, Digit Span, Picture Arrangement, Object Assembly, and Mazes (all measures related to temporal/parietal/frontal neurocognitive networks). Namely, MC WMH^+ performed better than WMH^- and not differently than CTL. Consequently, when the data are analyzed in this way, the test scores of the WMH^+ group seem better than expected (higher than those of the WMH^- group and comparable to CTL).

Inflammatory mediator data

IL-12p40, MCP1, CCL22, and TNF-α showed significant differences across the groups, while G-CFS showed a marginal difference (see Table 3). Regardless, the patterns of observed means are well described by quadratic models. Specifically, G-CFS and CCL22 had lower expression in MC WMH^- than the two other groups, which did not show significantly different expressions. For all other mediators, MC WMH^- reported a larger expression than the two other groups. Thus, WMH^- children had higher expression of TNF-α, MCP1, and IL-12p40, while exhibiting lower concentrations of G-CFS and CCL22.

DISCUSSION

WMH in children exposed to urban air pollution coexist with significant increases in gray and white matter volumes in target brain areas. WMH are

Table 3
Mean (standard errors) and contrast *t*-test statistics for the expression of inflammatory mediators in Mexico City children with white matter hyperintensities (MC WMH$^+$) and without (MC WMH$^-$) as compared to matched control children (CTL) from Polotitlán exposed to air pollution concentrations below the US standards

Inflammatory mediators	Group			SE	*t* (df = 27)
	MC WMH$^+$	*MC WMH$^-$*	*CTL*		
TNF α	8.62 (0.49)	10.54 (0.59)	9.63 (0.66)	1.44	2.60*
MCP1	104.27 (11.90)	127.64 (16.21)	74.22 (5.29)	31.01	2.50*
CCL22	1147.06 (144.04)	1066.69 (97.56)	1510.14 (153.94)	164.26	2.45*
G-CFS	3.56 (1.12)	2.07 (0.57)	5.01 (1.32)	1.04	2.13$^{\dagger a}$
IL-12p40	0.72 (0.16)	1.69 (0.57)	1.58 (0.47)	0.40	2.28^{*b}
White blood cells ($\times 10^3/\mu$L)	7340.0 ± 1793.3	6350.0 ± 835.7	8370.0 ± 1866.7		4.14*
Neutrophils total	3630.0 ± 1767.6	2790.0 ± 653.9	4540.0 ± 1274.7		4.44*
Monocytes total	480.0 ± 103.3	420 ± 91.9	480.0 ± 175.1		0.72

Note. *$p < 0.035$ (after Simes-Bonferroni correction for simultaneous multiple comparisons). Contrast weights were +1, −2, +1, for or MC WMH$^+$, MC WMH$^-$, and CTL groups, respectively; [a]df = 24 (due to unequal sample size adjustment); †$p = 0.043$; [b]df = 21 (due to unequal sample size adjustment).

correlated with better than expected cognitive outcomes and patterns of systemic inflammation significantly different from Mexico City children without WMH and control children. WHM$^+$ children display the profile of the M2 macrophage reparative response with low IL12, lower production of TNF-α and MCP-1, and general involvement in type II responses, immune regulation, and tissue remodeling [27]. On the other side of the spectrum, MC WMH$^-$ children exhibit a systemic inflammatory defensive response: high IL12, high production of powerful pro-inflammatory cytokines, low concentrations of CCL22 and G-CSF associated with decreased neuroprotection, along with the lower numbers of white blood cells and total peripheral neutrophils, evidence of the severe inflammation and endothelial activation [7, 27].

Systemic inflammation, respiratory tract inflammation, and endothelial activation are present in clinically healthy MC children in response to noxious particles and gases [5–7]. The high concentrations of the chemokine MCP-1 is particularly critical in view of its effect on the permeability of the blood-brain-barrier (BBB) [28]. MCP-1 is involved in the recruitment of both monocytes/macrophages and activated lymphocytes into the CNS and induces an increase in brain endothelial permeability. Since an intact BBB is key for proper functioning of neuronal circuits and synaptic transmission, the BBB breakdown in MC children could account for regional hypoxic conditions [29, 30]. MCP-1 is secreted by neurons and astrocytes following stroke and is well known to aggravate ischemia-related damage [31]. Equally important is the increased serum concentrations of TNF-α in exposed children [7], given the role of TNF-α as a marker of brain disease [32]. In adults, inflammatory markers like TNF are associated with decreases in total brain volume and in specific regions such as hippocampus [9, 33].

IL12, a cytokine with links to both innate and adaptive immunity systems, is a potent down-regulator of the expression of angiogenic chemokines CCL2 and CCL6 as well as other pro-angiogenic mediators including endoglin, HIF-1α, IL6, and VEGF-C [34]. IL12 has a critical role in inducing Th1 responses, which in turn increases the production of cytotoxic cytokines. The complex modulation of Th1 responses and angiogenesis-related genes is likely key for the decrease in gray and white matter volumes and high IL12 in MC WMH- children.

Macrophage specific chemokines include CCL22, a selective high affinity ligand at the CC chemokine receptor 4 (CCR4) with a strong T-helper 2 effect, and an important role in innate immunity directing the migration of monocytic cells into inflammatory sites [35]. CCL22 attracts T cells, leading to increased numbers of IL10 secreting T cells which in turn have anti-inflammatory properties [35]. The significantly low concentrations of CCL22 in MC WMH$^-$ children could go along with the lack of compensatory brain responses and the severe systemic inflammation, both contributing to the worse responses to the polluted environment. A cytokine growth factor that is significantly decreased in MC WMH$^-$ children is G-CSF, which induces the proliferation of endothelial cells, has immune modulatory effects on T cells, is neuroprotective in experimental stroke, and mobilizes CD34 (+) peripheral blood stem cells into the circulation [36]. The significant reduction of G-CSF signals can potentially decrease neuroprotection given by the diminished angiogenesis and neurogenesis associated

to activation of endothelial cells and mobilization of hematopoietic stem cells [36].

The neurovascular unit integrated by neurons, glia, and perivascular and vascular cells is a major target of air pollution in young children [2, 29]. The BBB is broken and there is endothelial hyperplasia and attachment of white blood cells to the activated endothelial cells with reduction of blood flow and ischemic white matter areas signaled by the presence of perivascular gliosis and perivascular trafficking of inflammatory cells [2, 29]. The homeostasis of the cerebral microenvironment is altered and the presence of WMH (indicators of microvascular injury) likely relates to vascular oxidative stress, endothelial dysfunction, and inflammation which in turn promote leakage, protein extravasation, and cytokine production [2, 29, 37]. White matter lesions disrupt saltatory conduction, slow the transmission of nerve impulses, give rise to a hypoxic environment, and compromise repair of the damaged white matter [38].

MC children exhibit supra and infratentorial inflammation and the white matter damage is likely diffuse. Considering that WMH^{+} children showed a number of increased gray and white matter volumes, as compared to WMH^{-}, one interpretation is that as WMH are associated with regional cerebral blood flow alterations; young brains could exhibit compensatory responses which would be also correlated with better than expected cognitive outcomes. Indeed, Kraut et al. [39] described cortical compensation mechanisms with increases in regional cerebral blood flow in elderly subjects without dementia and progressive WMH. Moreover, we know that endothelial cells play a key role in maintaining cerebral blood flow [40] and MC children have high concentrations of endothelin-1 [7]. Therefore, endothelial dysfunction and potent vasoconstriction may play a role in the pathogenesis of their WMH. Consequently, our tentative conclusion is that WMH^{+} may represent a disruption of the neurovascular unit in children still capable of responding to the injury with a compensatory increase of gray and white matter volume in key brain areas.

Indeed, increasing evidence shows that innate and inflammatory responses exhibit plasticity with resistance to or promotion of systemic damage, including brain diffuse damage in young children with high vulnerability. Anderson et al. [41] reviewed how both early plasticity and early vulnerability may reflect opposite extremes along a "recovery continuum" which, we argue, is pertinent to our MC children. The first parallel is the concept of early brain insult referring to insults in the preadolescent period when brain structures and their related neurobehavioral functions change rapidly. In our children, the detrimental effects likely start *in utero* and continue relentlessly as the child grows, such that the lesions are chronic, diffuse, and worsen with age [2, 19, 29]. Children's brains are fully capable of plastic change and neural compensation, thus the observation of increase in white matter volume in connection with a well defined vascular lesion associated with low blood flow [42] in otherwise healthy children is not surprising. Neural compensation has been described in association with WMH, frank brain lesions and in healthy subjects as a function of training and experience. Specifically, Duffau [43] detailed several compensation mechanisms following white matter damage (unmasking of peri-lesional latent networks, recruitment of accessory pathways, introduction of additional relays within the circuit, and involvement of parallel long-distance association pathways). If the child's responses to a single insult already depend on a complex set of factors (the nature of the insult, the severity, the timing, cognitive reserve, genetic makeup, nutrition status, family function, social status, etc.), the responses of a child continuously exposed to a polluted environment may even be more complex and his/her capacity to compensate and overcome the developmental disruption may be far more intricate given the neuroinflammation and early pathological markers of neurodegeneration [2].

We recognize our results are based on small samples—however, given the rigorous cohort selection, we are reasonably confident the data is representative of an urban Hispanic population with sustained air pollutant exposures and provides the basis for a larger longitudinal study to address the current limitations in knowledge.

In conclusion, we argue that a complex modulation of cytokines and chemokines influence children's WMH, brain volumetric responses, and cognition in the setting of sustained air pollution exposures. Since the presence of neocortical hyperphosphorylated tau suggests a link between oxidative stress, neuroinflammation, and neurodegeneration, a series of critical questions arise in this complex scenario:

What is the long term impact of WMH in clinically healthy children? What are the long term brain effects of the sustained inflammatory activity in a developing brain? Are the cognitive and volumetric changes reversible? Do the presence of hyperphosphorylation tau and diffuse amyloid plaques in exposed children herald an increased risk for AD? What do we tell the parents? And how are we going to protect these children?

Identification of air pollution exposed children at higher risk for neurodevelopmental deficits and neurodegenerative processes is critical. Early implementation of neuroprotective measures to ameliorate or stop the inflammatory and neurodegenerative processes is therefore warranted.

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