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Avaliação da exposição a poluentes inalatórios ambientais no período gestacional como fator de risco para dermatomiosite juvenil

Tese apresentada à Faculdade de Medicina da Universidade de São Paulo para obtenção do título de Doutor em Ciências

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Orientador: Prof. Dr. Clovis Artur Almeida da Silva

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Esta dissertação está de acordo com as seguintes normas, em vigor no momento desta publicação:

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São Paulo: Serviço de Biblioteca e Documentação; 2005.

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S U M Á R I O

LISTA DE ABREVIATURAS

ABIPEME	Associação Brasileira dos Institutos de Pesquisa de Mercados
AIJ	Artrite idiopática juvenile
AR	Artrite reumatoide
CETESB	Companhia Ambiental do Estado de São Paulo
CO	Monóxido de carbono
DMJ	Dermatomiosite juvenil
FTA	Fumaça do tabaco ambiental
HC-FMUSP	Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo
IC	Intervalo de confiança
LAPAE	Laboratório de Poluição Atmosférica Experimental da FMUSP
LES	Lúpus eritematoso sistêmico
NO	Óxido de nitrogênio
NO_2	Dióxido de nitrogênio
O_3	Ozônio
OR	*odds ratio*
PM_{10}	Material particulado inalável
SO_2	Dióxido de enxofre

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RESUMO

Orione MAM. Avaliação da exposição a poluentes inalatórios ambientais no período gestacional como fator de risco para dermatomiosite juvenil [tese]. São Paulo: “Faculdade de Medicina, Universidade de São Paulo”; 2014.

Objetivos: Avaliar a influência da exposição a fatores ambientais inalatórios durante a gravidez e o diagnóstico de dermatomiosite juvenil (DMJ). **Métodos:** Um estudo caso-controle incluiu 20 casos de DMJ e 56 controles, pareados por idade e sexo, residentes na região metropolitana de São Paulo. Através de um questionário foram obtidos os dados demográficos e os dados de exposição ambiental durante a gravidez: a exposição ocupacional (poeira causada por demolições, construções ou pedreiras, poeira de giz, tintas, verniz, vapor de combustível e fluídos de bateria), a existência de fontes de poluentes inalatórios próximas à residência da mãe e a exposição materna ao tabaco. As concentrações diárias de material particulado (PM_{10}), dióxido de enxofre (SO_2), dióxido de nitrogenio (NO_2), ozônio (O_3) e monóxido de carbono (CO) inalados foram avaliadas durante o período gestacional. **Resultados:** A exposição ocupacional materna a poeira de giz escolar e a resíduo volátil de gasolina ou diesel no grupo de DMJ foi significantemente maior comparada ao grupo controle (50% vs. 2,3%, p=0,004). Mães fumantes e exposição passiva ao cigarro na residência durante a gravidez foram significantemente maior no grupo de DMJ (20% vs. 1,7%, p=0,01; 35% vs. 16%, p=0,07, respectivamente). No modelo de regressão logística univariada, o fumo materno durante a gravidez, a exposição ocupacional a agentes inalados e a exposição ao CO troposférico no tercil mais elevado (3.2-5.4 ppm) no terceiro trimestre foram significantemente associados com DMJ (p<0,05). Na análise multivariada, o fumo materno (OR=13,26, IC 95% 1,21-144,29, p=0,03), a exposição ocupacional (OR=35,39, IC 95%1,97-632,80, p=0,01) e a exposição ao CO (terceiro tercil) no terceiro trimestre de gestação (OR=12,21, IC 95%1,28-115,96, p=0,03) permaneceram como fator de risco para DMJ. **Conclusão:** A exposição a poluentes inalatórios ambientais e fumaça de cigarro durante o desenvolvimento fetal podem contribuir para o aparecimento de DMJ.

Descritores: 1.Dermatomiosite; 2.Exposição ambiental; 3.Poluição do ar; 4.Tabaco; 5.Poluição por fumaça de tabaco; 6.Gravidez; 7.Criança; 8. Adolescente

ABSTRACT

Orione MAM. Exposure assessment to inhaled environmental pollutants in the pregnancy as risk factor for juvenile dermatomyositis [thesis]. São Paulo: "Faculdade de Medicina, Universidade de São Paulo"; 2014.

Objective: To evaluate the influence of exposures to inhaled environmental factors during pregnancy on juvenile dermatomyositis (JDM) diagnosis. **Methods:** A case-control study included 20 JDM and 56 healthy controls matched by age and gender residents in the metropolitan region of São Paulo city. A questionnaire assessed demographic data and environmental inhalation exposure during pregnancy (occupational exposure to demolition, chalk, construction and/or quarry dust, paints, varnish, fuel vapor and/or battery fluids, stationary sources of inhaled pollution near the mother's home and maternal tobacco exposure). Daily concentrations of inhaled particulate matter (PM_{10}), sulphur dioxide (SO_2), nitrogen dioxide (NO_2), ozone (O_3), and carbon monoxide (CO) were evaluated throughout the gestational period. **Results:** Maternal occupational exposure to chalk dust/gasoline vapor in JDM group was significantly higher compared to controls (50% vs. 2. 3%, p=0.004). Smoking mothers and secondhand smoke exposure at home during pregnancy were significantly higher in JDM group (20% vs. 1.7%, p=0.01; 35% vs. 16%, p=0.07; respectively). In univariate logistic regression models, maternal smoking, occupational exposure to inhaled agents and the higher tertile of trospospheric CO (3.2-5.4 ppm) in the third trimester were significantly associated with JDM ($p<0.05$). In multivariate analysis, smoking mother (OR=13.26, 95% CI 1.21-144.29, p=0.03), occupational exposure (OR=35.39, 95% CI 1.97-632.80, p=0.01) and CO (third tertile) exposure in the third trimester of gestation (OR=12.21, 95% CI 1.28-115.96, p=0.03) remained risk factors for JDM. **Conclusion:** Inhaled pollutants and tobacco smoking during fetal development may contribute to JDM.

Descriptors: 1.Dermatomyositis; 2.Environmental exposure; 3. Air pollution; 4.Tobacco; 5.Tobacco smoke pollution; 6.Pregnancy; 7.Children; 8. Adolescent

1. INTRODUÇÃO

A dermatomiosite juvenil (DMJ) é uma doença autoimune crônica, caracterizada pela perda de força muscular proximal e pela presença de lesões cutâneas, como consequência de uma vasculite sistêmica que acomete principalmente músculos e pele, mas que também pode acometer outros órgãos e sistemas. A DMJ responde por 85% dos casos de miopatias inflamatórias na infância, mas trata-se de uma doença rara, com incidência entre 2 a 3 casos/milhão de crianças/ano e de predominância no sexo feminino.[1,2]

Esta miopatia inflamatória idiopática é uma doença complexa, cuja patogênese envolve susceptibilidade genética[3] e inflamação vascular imunomediada em resposta a “gatilhos” como fatores ambientais[4], infecções virais ou bacterianas, uso de drogas, intervenções cirúrgicas[5], estresse emocional, vacinas, exercícios[6], exposição à luz ultravioleta e microquimerismo.[7,8]

Poluição do ar é a contaminação do ar por qualquer agente físico, químico ou biológico que altere as características da atmosfera. Consiste de uma mistura heterogênea de gases e partículas que incluem o ozônio (O_3), os óxidos de nitrogênio (NO, NO_2), o dióxido de enxofre (SO_2), o monóxido de carbono (CO), o material particulado inalável (PM_{10}) e produtos tóxicos da queima do tabaco.[9]

Os poluentes ambientais originam-se de uma variedade de fontes emissoras, sendo a queima dos combustíveis fósseis a principal, e podem ser classificados pela sua composição, tamanho ou pelo ambiente de

produção (*indoor* ou *outdoor*). Poluentes diretamente emitidos na atmosfera são chamados de primários enquanto poluentes que resultam de reações químicas com outros poluentes, ou reações fotoquímicas sob ação da radiação solar, são conhecidos como secundários.[9]

Os principais poluentes atmosféricos regulamentados e monitorados pelas agências ambientais reguladoras na maioria dos países, inclusive no Brasil, e preconizados pela Organização Mundial de Saúdes são: PM_{10}, SO_2, NO_2, CO e O_3.[9,10]

O NO_2 é um gás proveniente da combustão de combustíveis de origem fóssil, principalmente dos veículos automotores. O CO é formado durante a queima incompleta de combustíveis orgânicos como: óleo, gás natural, derivados outros do petróleo, carvão mineral e madeira. A queima de cigarro também é uma fonte de emissão de CO. Os veículos automotores contribuem com aproximadamente 60% das emissões. O O_3 é formado através de reações químicas envolvendo compostos orgânicos voláteis e óxidos de nitrogênio, sendo catalisadas pela luz solar. Nos períodos de grande incidência solar sua formação é ainda maior. O SO_2 é originado da queima de combustíveis fósseis. O PM_{10} é um termo geral que se refere a um composto de partículas líquidas e sólidas de diâmetro aerodinâmico inferior a 10µm (sendo consideradas finas <2.5µm e ultrafinas <0.1 µm), que ficam suspensas no ar. Estas partículas apresentam uma composição variada, com componentes orgânicos e inorgânicos (substâncias carbonáceas, elementos químicos, compostos orgânicos voláteis, entre outros, podem estar adsorvidos).[9,10]

A fumaça do tabaco ambiental (FTA) é composta por uma complexa mistura de aproximadamente 6000 substâncias químicas encontradas tanto na fase de vapor como na fase de partículas ultrafinas, e apresenta efeitos deletérios significativos sobre a saúde, os quais são observados também desde o intra-útero.[9]

Mesmo com determinações que regulam os níveis de concentração dos principais poluentes a níveis cada vez mais reduzidos nos grandes centros urbanos, os efeitos deletérios sobre a saúde humana persistem em várias etapas do desenvolvimento humano. O estudo da interface destes efeitos sobre as doenças inflamatórias sistêmicas tem crescido enormemente nas últimas décadas. A poluição troposférica pode ser um potencial contribuinte para o aparecimento das doenças autoimunes e das suas exarcebações,[9,10] especialmente a artrite reumatoide (AR) e o lúpus eritematoso sistêmico (LES).[9,11]

De fato, poluentes inalados exercem efeitos inflamatórios e causam estresse oxidativo no pulmão. Supõem-se que esta inflamação pulmonar local, após a exposição, seja somente um “gatilho” para a resposta inflamatória sistêmica e a ativação de mecanismos de autoimunidade, podendo desempenhar um papel nas doenças inflamatórias não-pulmonares mediadas por mecanismos imunológicos, como as doenças do tecido conectivo. Na vida intrauterina, a exposição da mãe a poluentes do ar pode também determinar agravos ao desenvolvimento fetal. [9,12]

Possivelmente a susceptibilidade a potenciais agentes ambientais dependa da predisposição genética individual, mas a confirmação de que agentes poluentes possam ter alguma contribuição no desencadeamento e ou perpetuação do processo inflamatório de doenças autoimunes poderia colaborar para o estudo de eventuais aumentos da incidência das doenças autoimunes ao longo dos anos, ou ao seu maior aparecimento em determinadas áreas geográficas, de acordo com a exposição a esses agentes, assim como a difusão de medidas de utilidade em termos prevenção.

Entretanto, até o presente momento, nenhum estudo avaliou a possível associação entre exposição à poluição do ar no período gestacional pelas mães dos pacientes com DMJ e o diagnóstico de dermatomiosite nestes pacientes. Portanto, o objetivo deste estudo foi avaliar a influência da exposição a fatores poluentes ambientais inalatórios durante a gravidez e o diagnóstico de DMJ em moradores de uma grande metrópole.

2. OBJETIVOS

1. Avaliar a exposição aos poluentes troposféricos no período gestacional e sua possível associação com o desenvolvimento de DMJ.

2. Avaliar a exposição à fumaça do tabaco ambiental no período gestacional, ativa ou passiva, como possível fator de risco para o desenvolvimento de DMJ.

3. Avaliar a exposição a fontes emissoras de poluentes presentes em um raio de até 500 metros dos locais de moradia da mãe durante a gravidez e sua possível associação com o desenvolvimento de DMJ.

4. Avaliar a exposição ocupacional a poluentes inalatórios pelas mães no período gestacional e sua possível associação com o desenvolvimento de DMJ.

3. MÉTODOS

3.1. Tipo de Estudo

Estudo tipo caso-controle.

3.2. População do Estudo

Entre agosto de 2011 e agosto de 2012, a Unidade de Reumatologia Pediátrica do Instituto da Criança do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HC-FMUSP) acompanhou 53 pacientes com DMJ que preenchiam critérios de Bohan e Peter[13]. Nós selecionamos 20 que residiram nos municípios da região metropolitana de São Paulo com monitoramento de poluição (São Paulo, São Caetano do Sul, Guarulhos, Santo André, São Bernardo do Campo, Diadema, Osasco, Taboão da Serra e Mauá) no período de tempo que precedeu o inicio da doença (média de 5,5 anos) e cujas mães também tinham residido nestas regiões monitoradas durante toda a gravidez.

O grupo controle foi composto de 56 crianças e adolescentes saudáveis, recrutados de ambulatórios de cuidados primários, não portadores de doenças inflamatórias crônicas, que residiram nestas regiões monitoradas no mesmo período, e cujas mães também tinham residido nestas áreas durante a gravidez.

Estes controles foram pareados por idades (3 anos a 5 anos e 11 meses; 6 anos a 8 anos e 11 meses; 9 anos a 11 anos e 11 meses; 12 anos a 14 anos e 11 meses; 15 anos a 17 anos e 11 meses; 18 anos a 20 anos e 11 meses) e por sexo.

Para a categorização socioeconômica dos participantes foram utilizados os critérios da ABIPEME - Associação Brasileira dos Institutos de Pesquisa de Mercados.[14]

O Termo de Consentimento Livre e Esclarecido e o Termo de Assentimento do Adolescente foram obtidos de todos os participantes e seus responsáveis legais.

O presente estudo foi aprovado pela Comissão de Ética para Análise de Projetos de Pesquisa do HCFMUSP (CAPPesq número 0899/08) e recebeu apoio do Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq 472155/2012-1 e 302724/2011-7 para CAAS), *Federico Foundation* para CAAS e do Núcleo de Apoio à Pesquisa “Saúde da Criança e do Adolescente” da USP (NAP-CriAd) para CAAS.

3.3. Questionário

Os dados relacionados aos fatores ambientais foram obtidos das mães dos pacientes com DMJ e das mães dos controles saudáveis por meio de um questionário estruturado. Nós adaptamos um questionário modificado a partir de um modelo usado previamente por Guimarães et al (2011),[15] incluindo as seguintes variáveis:

- Características sócio-demográficas
- Endereços de moradia das mães antes e durante a gravidez.
- Informações relacionadas ao trabalho das mães antes e durante a gravidez: tipo de trabalho, tipo de transporte e tempo para deslocamento entre a residência e o endereço do trabalho, exposição ocupacional a certos poluentes específicos (poeira de demolição, poeira de giz, resíduos de construções ou pedreiras, tintas, verniz, fluído de baterias e vapor de combustíveis como gasolina e óleo diesel)
- Informações sobre a existência de atividades industriais ou postos de combustíveis em um raio de 500 metros do local da residência.
- Uso de cigarros pela mãe (fumo ativo) ou outra pessoa residente no domicilio (fumo passivo) durante a gravidez

Entre agosto de 2011 e agosto de 2012, com o objetivo de avaliar a confiabilidade das respostas, um estudo piloto foi realizado com 20 mães que foram testadas, e posteriormente re-testadas 5 a 10 meses após o primeiro questionário. A realização do pré-teste permitiu adequar o questionário para melhor entendimento das questões pelos participantes, avaliar a consistência e a coerência das respostas. Este também permitiu estabelecer o tempo de preenchimento do mesmo, identificar questões duvidosas e corroborar a aplicabilidade e funcionalidade do banco de dados.

O mesmo pesquisador, após 5 a 10 meses, repetiu o preenchimento de questionário como re-teste para avaliar possível viés de memória. A confiabilidade do questionário como um instrumento adequado foi verificada com a realização do teste/re-teste e a aplicação do cálculo do índice de concordância de *Kappa*.

3.4. Dados dos Poluentes Troposféricos

As concentrações dos poluentes troposféricos foram fornecidas pela Companhia Ambiental do Estado de São Paulo (CETESB), que possui os

registros de 14 estações automáticas medidoras da poluição, distribuídas em diferentes partes da cidade.[16]

Todos os poluentes são mensurados por períodos de 24 horas. A CETESB fornece a medida diária de cada poluente aferido, considerando o período compreendido entre 16 horas do dia anterior e 15 horas do dia de referência, da seguinte maneira:

- PM_{10}: concentração média de 24 horas em $\mu g/m^3$
- SO_2: concentração média de 24 horas em $\mu g/m^3$
- NO_2: concentração da maior média horária em $\mu g/m^3$
- O_3: concentração da maior média horária em $\mu g/m^3$
- CO: concentração da maior média móvel em 8 horas em PPM

As características topográficas da região metropolitana de São Paulo dificultam a dispersão dos poluentes e os poluentes do ar registrados em cada estação são altamente correlacionados entre si, bem como as medidas de cada estação também apresentam alta correlação[17]. Portanto, a média dos valores de cada poluente aferida em todas as estações foi adotada como representativa da exposição em toda a região metropolitana. Estes registros encontram-se armazenados no Laboratório de Poluição Atmosférica Experimental da FMUSP – LAPAE.

3.5. Análise Estatística

A análise descritiva incluiu as variáveis contínuas apresentadas em medidas de tendência central e dispersão (média ± desvio padrão ou mediana e variação), e as variáveis categóricas apresentadas em valores absolutos e relativos no grupo de casos e no grupo controle.

Os dados foram comparados pelos testes *t-Student* ou *Mann-Whitney* para as variáveis contínuas, e pelo teste do *chi-quadrado* ou teste exato de *Fischer* para as variáveis categóricas.

As concentrações médias de cada poluente troposférico durante a gravidez (período total da gravidez, primeiro trimestre, segundo trimestre e terceiro trimestre) foram calculadas e categorizadas em *tercis* para cada participante, em cada um dos períodos.

De acordo com as características de exposição, pelas informações obtidas através do questionário, nós definimos quatro grupos de variáveis independentes:

1. Tabagismo materno e exposição passiva (fumo pelo companheiro/marido/pai ou outra pessoa residente na casa) - dicotômica

2. Exposição ocupacional dos pais a um dos seguintes agentes inalados: poeira de demolição/construção/pedreiras ou poeira de giz escolar e componentes voláteis (tintas, verniz, fluído de baterias e resíduos de combustíveis) - dicotômica
3. Distância em metros entre a residência e fontes de poluentes inalatórios presentes no ambiente, incluindo postos de gasolina, indústrias e pedreiras (< 100, 100-200 e > 200 metros);
4. Exposição no tráfego, baseado em tempo necessário para o deslocamento diário do local de moradia até o local de trabalho da mãe (<30, 30-60 e > 60 minutos), e cinco indicadores de exposição a poluentes troposféricos em cada trimestre da gravidez (exposição ao PM_{10}, SO_2, NO_2, O_3 e ao CO).

Nós adotamos os modelos de regressão logística para identificar fatores de risco para o desenvolvimento de DMJ. No modelo multivariado nós usamos como variáveis independentes aquelas que apresentaram um nível de significância menor que 20% no modelo univariado. Os resultados do modelo de regressão foram apresentados como *odds ratio* (OR) e intervalo de confiança (IC) de 95%. Em todos os testes estatísticos o nível de significância foi fixado em 5% ($p<0,05$). O programa usado para as análises estatísticas foi IBM-SPSS-20.

4. RESULTADOS

O índice *kappa* para o teste-reteste foi de 0,81, demonstrando alto grau de concordância nas respostas maternas e excelente confiabilidade do instrumento.

Pacientes com DMJ e controles foram comparáveis em relação à média de idade cronológica (12,62 ± 3,54 anos vs. 12,05 ± 3,49 anos, p=0,33), e frequência do sexo feminino (60% vs. 56%, p=0,57).

A mediana de idade de aparecimento do primeiro sintoma antes do diagnóstico de DMJ foi de 5 anos (1-10) e a mediana de idade do diagnóstico foi de 6 anos (1-10). Nenhuma diferença foi evidenciada entre as classes socioeconômicas C ou D em ambos os grupos (55% vs. 34%, p=0,12).

Em relação aos fatores ambientais inalatórios, a frequência de mães no grupo de casos e no grupo controle que residiam no mesmo endereço durante a gestação foi semelhante (85% vs. 91%, p=1,0). Somente 30% das mães trabalhavam fora do domicílio durante a gestação no grupo de DMJ, comparado com 76% das mães do grupo controle (p<0,001). Entretanto, a exposição ocupacional (à poeira de giz escolar ou a vapor de gasolina/diesel) durante a gravidez nas mães do grupo de DMJ que trabalhavam fora do domicílio foi significantemente maior quando comparada com as mães que trabalhavam no grupo controle (50% vs. 2.3%, p=0,004).

No modelo de regressão logística univariada, uma associação foi observada entre exposição ocupacional das mães durante a gravidez e o diagnóstico de DMJ (OR=9,70, IC 95% 0,94-99,51, p=0,05).

Quando analisadas as distâncias entre a residência e indústrias e entre a residência e postos de combustíveis durante a gravidez, os resultados foram semelhantes nos dois grupos: 0-100 metros (15% vs. 10,7%, p=0,69); 100-200 metros (20% vs. 17,8%, p=0,99) e > 200 metros (50% vs. 55,4%, p=0,80). No modelo de análise univariada, nenhuma associação com significância menor que 20% foi observada entre estas variáveis e o diagnóstico de DMJ.

A presença de mães fumantes (tabagismo materno ativo) e a exposição passiva a outros fumantes na casa (tabagismo materno passivo), durante a gravidez foram maiores no grupo de DMJ comparado com o grupo controle (20% vs. 1,7%, p=0,01; 35% vs. 16%, p=0,07 respectivamente). No modelo de regressão logística univariada, uma associação foi observada entre tabagismo materno durante a gravidez e o diagnóstico de DMJ (OR=13,75, IC 95% 1,43-131,9, p=0,02).

Conforme os dados de exposição ao tráfego, o tempo utilizado para o deslocamento de casa ao trabalho durante a gravidez foi similar no grupo de DMJ *versus* controles: < 30 minutos (15,6% vs. 35,7%, p=0,97), 30-60 minutos (15,6% vs. 26,8%, p=0,37) e > 60 minutos (5% vs. 10,7%, p=0,33). No modelo de regressão logística univariada, uma associação com nível de

significância menor que 20% foi observada somente entre tempo menor que 30 minutos e o diagnóstico de DMJ (OR=0,31, IC 95% 0,83-1,21, p=0,09).

Em relação aos poluentes troposféricos (O_3, PM_{10}, NO_2, SO_2 e CO), nenhuma associação foi evidenciada entre a exposição à concentração média de cada um, no período total da gravidez, e o diagnóstico de DMJ (p>0,05). Entretanto, quando se analisaram a exposição por trimestres da gravidez, a exposição ao O_3 (segundo tercil= 69,6-85,0 µg/m^3) no primeiro trimestre (OR=0,10, IC 95% 0,01-0,96, p=0,04), ao O_3 (terceiro tercil= 84,4-122,0 µg/m^3) (OR=0,16, IC 95% 0,03-0,72, p=0,02) e ao CO (terceiro tercil= 3,2-5,2 ppm) (OR=5,71, IC 95% 1,06-30,63, p=0,04) no segundo trimestre, bem como a exposição ao CO (terceiro tercil=3,2-5,4 ppm) no terceiro trimestre (OR=7,69, IC 95% 1,44-40,90, p=0,02) foram associadas com o diagnóstico de DMJ.

Em relação a estas variáveis de exposição ao tráfego, avaliando em um modelo de regressão múltipla a variável tempo de deslocamento da casa ao trabalho e os poluentes troposféricos que apresentaram associação na análise univariada, somente o CO do terceiro trimestre (OR=6,90, IC 95% 1,27-37,39, p=0,03) e o O_3 no segundo trimestre (OR=0,17, IC 95% 0,37-0,77, p=0,02) permaneceram significantes. Quando os efeitos destes dois poluentes foram determinados pelo mesmo modelo de regressão, somente o CO do terceiro trimestre permaneceu como fator de risco significante.

Em uma avaliação final, com um modelo de regressão multivariada incluindo o tabagismo materno, a exposição ocupacional materna e a exposição ao CO no terceiro trimestre da gravidez, os três foram fatores de risco para DMJ (Tabela 1).

Tabela 1 – Exposição ao tabaco, exposição ocupacional e exposição ao CO durante a gestação como fator de risco para dermatomiosite juvenil em modelo de regressão múltipla.

Variáveis independentes	**OR**	**IC 95%**	***p***
Tabagismo materno	13,26	1,21 – 144,29	0,03
Exposição ocupacional à poeira de giz ou vapor de combustível	35,39	1,97 – 632,80	0,01
CO (ppm) em *tercis* no terceiro trimestre de gravidez			
Primeiro *tercil* (1,3 - 2,45)	1,00	-	-
Segundo *tercil* (2,36 – 3,17)	4,05	0,39 – 41,82	0,29
Terceiro *tercil* (3,18 – 5,35)	12,21	1,28 – 115,96	0,03

CO = monóxido de carbono, OR = *Odds ratio*, IC = intervalo de confiança

5. DISCUSSÃO

Este foi o primeiro estudo que identificou que a exposição aos poluentes do ar durante a gestação pode contribuir para o inicio de DMJ em moradores de uma grande metrópole, principalmente a exposição aos poluentes troposféricos e à fumaça do cigarro.

A principal vantagem do presente estudo foi utilizar como instrumento um questionário estruturado incluindo questões relacionadas à exposição inalatória ambiental durante a gravidez.[15] Para reduzir os efeitos de viés de memória das mães, aplicou-se o cálculo do índice de *kappa* no estudo piloto de teste-reteste, que indicou uma excelente confiabilidade de respostas para este grupo.

Além disso, as concentrações dos poluentes troposféricos foram avaliadas pelas medidas obtidas sistematicamente das estações automáticas de monitorização ao longo da cidade.

Entretanto, a principal limitação do estudo foi o reduzido número de pacientes com DMJ, com critérios restritos, principalmente devido à inclusão apenas de residentes na área metropolitana monitorada de São Paulo, e o fato de que a medida das estações de monitoramento da poluição não reflete completamente a exposição à poluição de cada individuo.

A poluição do ar consiste de uma mistura heterogênea de componentes que incluem CO e material particulado. Poucos estudos têm demonstrado uma associação entre exposição à poluição do ar e o

desenvolvimento de doenças autoimunes em crianças. Zeft et al, em um estudo de caso-controle conduzido em Utah, Estados Unidos da América, avaliou a associação entre concentração de material particulado fino e o início dos sintomas em pacientes com artrite idiopática juvenil (AIJ). Foi observado um alto risco de AIJ em crianças menores de cinco anos associado com altas concentrações de $PM_{2,5}$ e condições de ar estagnado nos 14 dias que precederam o quadro clínico (RR=1,60, IC 95% 1,00-2,54). Entretanto, os autores não avaliaram nenhuma outra exposição ambiental além do material particulado fino (outros poluentes ou fumaça de cigarro).[11]

Estudos envolvendo os componentes troposféricos, tanto estudos epidemiológicos como experimentais, descrevem a relação entre estresse oxidativo, inflamação sistêmica e autoimunidade.[9,10] Com relação a este aspecto, no presente estudo a exposição das mães a alguns poluentes do ar, particularmente no terceiro trimestre de gestação, pode contribuir para o desenvolvimento da DMJ.

Interessantemente, Vegosen et al avaliaram as condições de nascimento de pacientes com miopatia inflamatória idiopática para verificar a influência da sazonalidade da exposição ambiental inicial (no momento do nascimento) no desenvolvimento posterior desta doença autoimune. Foi demonstrado que a distribuição sazonal dos nascimentos apresentou forte relação com certos grupos de miosite inflamatória juvenil, o que não ocorreu no grupo de adultos, sugerindo que a exposição ao ambiente perinatal pode influenciar o início da doença em crianças.[18] Por outro lado, estudos têm

mostrado que uma única[8] ou várias exposições ambientais[3,7]foram associadas com a DMJ, particularmente nos seis meses que antecedem o início dos sintomas.[6]

Entretanto, nenhum destes estudos avaliou fatores ambientais durante o desenvolvimento fetal na população de pacientes com DMJ.

No presente estudo, a exposição ocupacional à poeira de giz escolar ou a resíduos voláteis de gasolina/óleo diesel *outdoor* durante a gravidez foi um fator de risco para DMJ. De fato, poluentes inalatórios incluídos no material particulado fino, como a sílica, podem causar doenças reumatológicas autoimunes.[19,20] A exposição à sílica é tóxica para macrófagos.[21,22] e pode induzir apoptose com exposição de auto-antígenos intracelulares.[23-25] Estudos experimentais sugerem que a sílica pode então induzir autoimunidade.[24,26]

Adicionalmente, a fumaça do tabaco pode induzir inflamação e autoimunidade.[27,28] O fumo ativo de cigarros tem sido reconhecido como um fator de risco para o desenvolvimento de AR e LES.[29] Interessantemente , assim como foi observado neste estudo, fumo materno durante a gravidez foi um determinante fator de risco associado ao desenvolvimento de AR e AIJ nos primeiros anos de vida.[27]

Microquimerismo é a transferência de células entre mãe e filho durante a gravidez.[7,30] Uma elevada quantidade de células maternas nos linfócitos de sangue periférico e no tecido muscular afetado foram relatadas

em pacientes com DMJ.[31] O possível papel da poluição do ar e do uso de cigarros pela mãe no microquimerismo materno, deflagrando DMJ, é um aspecto relevante e deverá ser estudado futuramente.

Recentemente, Yamamoto et al sugeriram que o CO altera os níveis de metilação da proteína histona H3, indicando a possibilidade de que este poluente do ar pode provocar modificação epigenética.[32] A regulação epigenética consiste na interação entre gene e ambiente e futuros estudos são necessários em pacientes com DMJ.[26]

Além disso, outros estudos avaliando a exposição aos poluentes troposféricos no período pré e pós-gestacional e sua possível associação com o desenvolvimento de DMJ também serão realizados, assim como com outras doenças autoimunes reumatológicas (LES e AIJ).

Neste estudo exploratório, poluentes gerados pelo tráfego como o CO, a fumaça de tabaco e a exposição ocupacional a poeira de giz escolar e/ou resíduos voláteis de combustíveis durante o desenvolvimento fetal podem contribuir para o desenvolvimento de DMJ.

Assim sendo, minimizar a exposição aos poluentes do ar deve ser uma prioridade de saúde pública, especialmente para moradores de grandes cidades.

6. CONCLUSÕES

1. A exposição ao CO troposférico no terceiro trimestre da gestação foi fator de risco para o desenvolvimento de DMJ.

2. O tabagismo materno durante a gestação foi fator de risco para o desenvolvimento de DMJ.

3. A presença de fontes emissoras de poluentes ambientais presentes próximo aos locais de moradia da mãe durante a gravidez (postos de combustíveis e/ou industrias em um raio de 500 metros), não mostrou associação com o desenvolvimento de DMJ.

4. A exposição à poeira de giz e/ou resíduos voláteis de combustíveis no local de trabalho das mães durante a gestação foi fator de risco para DMJ.

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ANEXOS

Anexo I - Risk factors for juvenile dermatomyositis: exposure to tobacco and air pollutants during pregnancy
Artigo submetido para publicação

Anexo II – "Air pollution in autoimmune rheumatic diseases: A review"
Publicado na revista *Autoimmunity Reviews*

RISK FACTORS FOR JUVENILE DERMATOMYOSITIS: EXPOSURE TO TOBACCO AND AIR POLLUTANTS DURING PREGNANCY

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ABSTRACT

Objective: To evaluate the influence of exposures to inhaled environmental factors during pregnancy on juvenile dermatomyositis (JDM) diagnosis. **Methods:** A case-control study comprising 20 JDM and 56 healthy controls matched by age and gender residents in the metropolitan region of a large city. A questionnaire assessed demographic data and environmental inhalation exposure during pregnancy (occupational exposure to demolition, chalk, construction and/or quarry dust, paints, varnish, gasoline vapor and/or battery fluids, stationary sources of inhaled pollution near the mother's home and maternal tobacco exposure). Daily concentrations of inhaled particulate matter (PM_{10}), sulphur dioxide(SO_2), nitrogen dioxide(NO_2), ozone (O_3), and carbon monoxide (CO) were evaluated throughout the gestational period. **Results:** Maternal occupational exposure to chalk dust/gasoline vapor in JDM group was significantly higher compared to controls (50% vs. 2.3%, p=0.004). Smoking mothers and secondhand smoke exposure at home during pregnancy were significantly higher in JDM group (20% vs. 1.7%, p=0.01; 35% vs. 16%, p=0.07; respectively). In univariate logistic regression models, maternal smoking, occupational exposure to inhaled agents and the higher tertile of trospospheric CO (3.2-5.4 ppm) in the third trimester were significantly associated with JDM ($p<0.05$). In multivariate analysis, smoking mother (OR=13.26, 95%1.21-144.29, p=0.03), occupational exposure (OR=35.39, 95%CI 1.97-632.80, p=0.01) and CO (third tertile) exposure in the third trimester of gestation (OR=12.21, 95%CI 1.28-115.96, p=0.03)

remained risk factors for JDM. **Conclusion:** Inhaled pollutants and tobacco smoking during fetal development may contribute to JDM.

Keywords: juvenile dermatomyositis, environmental factor, smoking, pregnancy, air pollution.

Word Count: 2252

INTRODUCTION

Juvenile dermatomyositis (JDM) is a rare chronic autoimmune disease characterized by weakness of proximal muscles and skin rashes.[1,2] This idiopathic inflammatory myopathy is a complex genetic disease[3] that occurred in susceptible subjects in response to environmental triggers,[4] such as viral and bacterial infections, drugs, medical devices,[5] emotional stress, vaccines, exercise,[6] microchimerism and exposure to ultraviolet light.[7, 8]

Additionally, tropospheric pollution may be a potential contributor to autoimmune diseases onset and flare, especially rheumatoid arthritis and systemic lupus erythematosus.[9-11] Air pollution is composed of a heterogeneous mixture of gases and particles that include ozone (O_3), particulate matter (PM_{10}), nitrates (NO), sulphur dioxide (SO_2), toxic by-product of tobacco smoke and carbon monoxide (CO) and may trigger systemic inflammation and autoimmunity.[9,12]

However to our knowledge, no study has evaluated the possible association between exposure to air pollution during mothers' pregnancy and JDM patients' diagnosis. Therefore, the aim of this study was to assess the influence of exposures to inhaled environmental factors during pregnancy on JDM diagnosis in residents of a large metropolitan city.

METHODS

This is an exploratory case-control study. From August 2011 to August 2012, the Pediatric Rheumatology Unit of the Children's Institute, Faculdade

de Medicina da Universidade de São Paulo, Brazil followed 53 JDM patients that fulfilled the Bohan and Peter criteria.[13] We selected 20 of them who were residents in the metropolitan region of São Paulo, where air pollution was monitored in the time period preceding the disease onset, and whose mothers had resided in this region during pregnancy.

The control group was composed of 56 healthy children and adolescents recruited from the primary care clinic, without chronic inflammatory diseases and with the same inclusion criteria. Socioeconomic status was classified by the Brazilian Association of Market Research Institutions (ABIPEME - Associação Brasileira dos Institutos de Pesquisa de Mercados).[14] Local Ethics Committee of our University Hospital approved this study and informed consent was obtained from all participants and their legal guardians.

1. **Structured questionnaire to assess inhaled environmental factors**

The data were obtained from JDM patients and healthy controls mothers by means of a structured questionnaire. We adopted a questionnaire modified from that used by Guimarães et al (2011),[15] including the following variables:

- Socio-demographic characteristics;
- Mothers' address before and during JDM and control pregnancies;
- Mother's occupation before and during JDM and control pregnancies (mother's occupation; time taken to commute from home to workplace; occupational exposure for specific pollutants:

demolition, school chalk, construction and/or quarry dust, paints, varnish, gasoline vapor and/or battery fluids);

- Information of industrial activities or gas station within a radius of up to 500 meters from the residence;
- Use of cigarettes by the mother, father or other resident during pregnancy.

From August 2011 to August 2012 in order to evaluate response reliability, a pilot study was carried out with 20 consecutive mothers' who were tested and then retested 5 to 10 months later after the first questionnaire,

2. Tropospheric pollutants data

Daily data of studied pollutants, including O_3 (the highest hourly average), SO_2 (24-hour average), NO_2 (the highest hourly average), PM_{10} (24-hour average) and CO (the highest 8-hour moving average) were obtained for the entire study period from the Sao Paulo State Environmental Agency (CETESB) from fourteen automated pollution monitoring stations in different part of the city.[16] All pollutants were measured throughout a 24 hour period. The average of all the stations that measured each pollutant was adopted as an exposure status throughout the city, since air pollutants levels recorded in each station were highly correlated.[17]

3. Statistical analysis

The test-retest reliability of the questionnaire was verified using the kappa index. Descriptive analyses included continuous variables (mean ± standard deviation or median and range) and categorical variables (%) in JDM and healthy control groups. Data were compared by t-Student or Mann-Whitney tests for continuous variables. Categorical variables were assessed by chi-square test or Fisher's exact test. The average concentration of each tropospheric pollutant in pregnancy (total period of pregnancy, first trimester, second trimester and third trimester) was calculated and categorized into tertiles for each participant. According to the characteristics of exposure assessed through the questionnaire we defined four groups of independent variables:

1. Maternal smoking and secondhand smoke exposure at home (husband or other people) (dichotomous);
2. Parents occupational exposure to any of the following inhaled agents (dichotomous): demolition/construction or school chalk dust and volatile components;
3. Home distance to environmental sources of inhaled pollutants including gas stations, industries and quarry (< 100, 100-200 and > 200 meters);
4- Traffic exposure based on: time taken to commute from home to work (<30, 30-60 and > 60 minutes) and five indicators of the

exposure to tropospheric pollutants in each pregnancy trimester.

We adopted logistic regression models to identify risk factors for JDM. In the multiple model, we used as independent variables those that presented a level lower than 20% of significance in single model. Results of the regression models were presented as odd ratio (OR) and 95% of confidence interval (CI). In all the statistical tests the level of significance was set at 5% ($p < 0.05$). The IBM-SPSS-20 program was used for the statistical analyses.

RESULTS

The kappa index for test-retest was 0.81 thus demonstrating excellent reliability for the mothers' responses.

The current age was similar between JDM patients and healthy controls (12.62 ± 3.54 years vs. 12.05 ± 3.49 years, p=0.33), likewise the frequency of female gender (60% vs. 56%, p=0.57). The median of first symptom and JDM diagnosis was 5 years (range 1-10). The median of age at diagnosis was 6 years (range 1-10). No differences were evidenced between the C or D socio economic classes in both groups (55% vs. 34%, p=0.12).

Regarding the inhaled environmental factors, the frequency of mothers' of JDM and control groups that resided at the same address during pregnancy was comparable (85% vs. 91%, p=1.0). Only 30% of the mothers worked during pregnancy in the JDM group compared to 76% of controls

(p<0.001). However, the occupational exposure (school chalk dust or gasoline vapor) during pregnancy in JDM group working mothers was significantly higher compared to controls working mothers (50% vs. 2.3%, p=0.004). In univariate logistic regression models, an association was observed between mother's occupational exposure during pregnancy and JDM diagnosis (OR=9.70, 95% CI 0.94-99.51, p=0.05).

Distance from home to industries and from home to gas station during pregnancy in JDM group and controls were alike in two groups: 0-100 meters (15% vs. 10.7%, p=0.69); 100-200 meters (20% vs. 17,8%, p=0.99) and > 200 meters (50% vs. 55,4%, p=080). In univariate logistic regression models, no association with significance less than 20% was observed between these variables and JDM diagnosis.

Maternal smoking and secondhand smoke exposure at home during pregnancy were higher in JDM group compared to controls (20% vs. 1.7%, p=0.01; 35% vs. 16%, p=0.07 respectively). In univariate logistic regression models, an association was observed between maternal smoking during pregnancy and JDM diagnosis (OR=13.75, 95%CI 1.43-131.9, p=0.02).

According to the traffic exposure data, the time taken to commute from home to workplace during pregnancy was similar in JDM group *versus* controls: < 30 minutes (15.6% vs. 35.7%, p=0.97), 30-60 minutes (15.6% vs. 26.8%, p=0.37) and > 60 minutes (5% vs. 10.7% p= 0.33). In the univariate logistic regression models, an association with significance level less than 20% was observed only between the time taken under 30 minutes and JDM diagnosis (OR. 0.31, 95% CI 0.83-1.21, p=0.09).

Regarding tropospheric pollutants (O_3, PM_{10}, NO, SO_2 and CO), no association was evidenced between the average exposure to each air pollutant in the total period of pregnancy and JDM diagnosis ($p>0.05$). However, when we analyzed the exposure according to trimesters of pregnancy, O_3 (second tertile= 69.6-85.0 $\mu g/m^3$) in the first trimester of pregnancy (OR=0.10, 95%CI 0.01-0.96, p=0.04), O_3 (third tertile= 84.4-122.0 $\mu g/m^3$) In the second trimester of pregnancy (OR=0.16, 95%CI 0.03-0.72, p=0.02) and CO (third tertile= 3.2-5.2 ppm) in the second trimester (OR=5.71, 95%CI 1.06-30.63, p=0.04), as well as exposure to CO (third tertile=3.2-5.4 ppm) in the third trimester (OR=7.69, 95%CI 1.44-40.90, p=0.02) were associated with JDM diagnosis.

Regarding traffic exposure variables, in air pollutant-specific regression models with time taken to commute from home to workplace during pregnancy, only CO of third trimester (OR=6.90, 95%CI 1.27-37.39, p=0.03) and O_3 at second trimester (OR= 0.17, 95%CI 0.37-0.77, p=0.02) remained significant. When we assessed the effects of the two pollutants that maintained statistical significance in the same regression model, only CO of third trimester remained significant as risk factor (OR=5.98, 95% CI 1.06-33.71, p=0.04).

Table 1 shows results of a multiple regression model including maternal smoking, maternal occupational exposure and CO on the third trimester of pregnancy as risk factors for JDM in a multivariate analysis. We observed that those three variables remained independent and significant risk factors for JDM.

DISCUSSION

To our knowledge, this was the first study to identify that exposure to air pollutants during pregnancy may have contributed to the JDM onset in residents of a large city, mainly tropospheric pollutants and smoking.

The main strength of the present study was a structured questionnaire including questions regarding the environmental inhalation exposure during pregnancy.[15] In order to reduce the mothers' effects of memory bias, we observed a high kappa index for the pilot study test-retest, which indicated an excellent response reliability for this group. In addition, tropospheric pollutants were systematically assessed from automated monitoring stations in a large city. However, the main weakness was the small population of JDM based on these restricted criteria, mainly due to the inclusion of residents in the São Paulo metropolitan area, and the fact that pollution monitoring stations did not fully reflect the pollution exposure of each individual.

Air pollution consists of a heterogeneous mixture of gases that include CO and particles. Few studies have demonstrated an association between exposure to air pollution and the development of autoimmune diseases in children. Zeft et al, in a case-crossover study conducted in Utah, USA, evaluated the association between concentrations of fine particulate matter and the onset of symptoms in JIA patients. It was observed a high risk of JIA onset in children under five years associated with higher concentrations of $PM_{2,5}$ and stagnant air conditions in the preceding 14 days (RR=1.60, 95% CI

1.00–2.54). However the authors did not evaluate any other environmental exposures, including tobacco smoke.[11]

Tropospheric epidemiological and experimental studies describe the relation between oxidative stress, systemic inflammation and autoimmunity.[9, 10] In this regard, the mother' exposure to this air pollutant observed in the present study, particularly in the third trimester of pregnancy, may contribute to the JDM onset.

Interestingly, Vegosen et al evaluated the conditions of birth of patients with idiopathic inflammatory myopathy to verify the influence of seasonal early environmental exposure in the later development of this autoimmune disease. It was demonstrated that for certain groups of juvenile inflammatory myositis, the distribution of births presented stronger seasonal effects than in the adult group, suggesting that perinatal environmental exposure may influence the onset of the disease in childhood.[18] On the other hand, studies had demonstrated that single[8] and several environmental exposures[3-7] were associated with JDM, particularly in the last six months before disease onset.[6] However to our knowledge, none of these studies assessed environmental factors during fetal development in JDM population.

Of note, occupational exposure due to school chalk dust or outdoor gasoline vapor during pregnancy was a risk factor for JDM. Indeed, inhaled pollutants included fine particulate matter, such as silica, may cause rheumatic autoimmune diseases.[19-22] Exposure to silica is toxic on macrophages,[22,23] and may induce apoptosis and exposure of intracellular

self-antigens.[23] Experimental studies suggest that silica triggers autoimmunity.[24-26]

Additionally, tobacco smoking may induce inflammation and autoimmunity.[27-29] Active cigarette smoking has been recognized as a risk factor for rheumatoid arthritis and systemic lupus erythematosus developments.[29] Interestingly as observed herein, maternal smoking in pregnancy was a determinant risk factor associated with the development of rheumatoid arthritis and juvenile idiopathic arthritis during the first years of life.[27]

Microchimerism is a transfer of cells between mother and child during pregnancy.[7,30] Elevated maternal cells in peripheral blood lymphocyte and affected muscle tissue were reported in JDM patients.[31] The possible role of air pollution and smoking in maternal microchimerism triggering JDM should also be studied.

Recently, Yamamoto el al. suggest that CO changes methylation levels of protein histone H3, suggesting the possibility that this air pollutant may provoke epigenetic modification.[32] Epigenetic regulation is the link between gene and environment interaction, and further studies are also required in JDM patients.[26]

In conclusion, in this exploratory study, traffic generated pollutant as CO, tobacco smoking and occupational exposure to school chalk dust or/and gasoline vapor during fetal development may contribute to JDM. Consequently, minimizing exposure to air pollution should be taken into account, especially for patients residing in large cities.

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CONFLICTS OF INTEREST: none

Table 1 – Exposure to tobacco and inhaled pollutants during gestation as risk factors for juvenile dermatomyositis in multiple regression model.

Independent variables		**OR**	**95% CI**	**p**
Smoking mother		13.26	1.21 -144.29	0.03
Occupational exposure chalk dust or gasoline vapor		35.39	1.97 - 632.80	0.01
Tertiles of CO (ppm) third trimester of pregnancy				
	First (1.3- 2.45)	1,00	-	-
	Second (2.46- 3.17)	4.05	0.39- 41.82	0.29
	Third (3.18- 5.35)	12.21	1.28 -115.96	0.03

OR – *Odds ratio*; CI - confidence interval.

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Review

Air pollution in autoimmune rheumatic diseases: A review

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ABSTRACT

Air pollution consists of a heterogeneous mixture of gasses and particles that include carbon monoxide, nitrates, sulfur dioxide, ozone, lead, toxic by-product of tobacco smoke and particulate matter. Oxidative stress and inflammation induced by inhaled pollutants may result in acute and chronic disorders in the respiratory system, as well as contribute to a state of systemic inflammation and autoimmunity. This paper reviews the mechanisms of air contaminants influencing the immune response and autoimmunity, and it focuses on studies of inhaled pollutants triggering and/or exacerbating rheumatic diseases in cities around the world. Remarkably, environmental factors contribute to the onset of autoimmune diseases, especially smoking and occupational exposure to silica in rheumatoid arthritis and systemic lupus erythematosus. Other diseases such as scleroderma may be triggered by the inhalation of chemical solvents, herbicides and silica. Likewise, primary vasculitis associated with anti-neutrophil cytoplasmic antibody (ANCA) may be triggered by silica exposure. Only few studies showed that air pollutants could trigger or exacerbate juvenile idiopathic arthritis and systemic lupus erythematosus. In contrast, no studies of tropospheric pollution triggering inflammatory myopathies and spondyloarthropathies were carried out. In conclusion, air pollution is one of the environmental factors involved in systemic inflammation and autoimmunity. Further studies are needed in order to evaluate air pollutants and their potentially serious effects on autoimmune rheumatic diseases and the mechanisms involved in the onset and the exacerbation of these diseases.

Contents

1. Introduction

Several factors may influence the disease onset or its exacerbations, triggering autoimmune diseases in genetically susceptible patients [1,2]. Infections [3,4] primary immunodeficiency [5], immune

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adjuvant [6,7] and other environmental factors can trigger these disorders. Of note, Shoenfeld and Agmon-Levin [6] reviewed the pathogenesis of four immune mediated diseases triggered by exposure to immune adjuvants (silicone, aluminum salts, pristane and infectious components). The authors found out that these diseases shared similar symptoms and signs and suggested to include these disorders under a common syndrome: ASIA [Autoimmune (Auto-inflammatory) Syndrome Induced by Adjuvants]. The study suggested that these disorders occurred only in subjects who are genetically susceptible or they may occur in conditions where there is co-exposure to more than one adjuvant or to another environmental factor. In this way, the knowledge of new environmental factors and their possible mechanisms to trigger autoimmunity is an interesting theme. Remarkably, one of the possible environmental factors involved in autoimmunity and systemic inflammation is air pollution.

2. Could air pollution generate systemic inflammation?

Air pollution consists of a heterogeneous mixture of gasses and particles that include carbon monoxide (CO), nitrates (NO_X), sulfur dioxide (SO_2), ozone (O_3), lead, toxic by-product of tobacco smoke and particulate matter (PM). Particulate matter is composed of solid and liquid particles [8].

The association of the effects of tropospheric pollution on mortality and cardiovascular and respiratory morbidity has been identified in developed [8–13] and developing countries [14,15]. Our Environmental Epidemiology Study Group in São Paulo, Brazil demonstrated that air pollution is still a public health hazard [16–19].

Many of the harmful effects on human health caused by tropospheric pollutants have been linked to particles smaller than 10 μm (micrometers) in diameter (fine and ultrafine particulate matter). These particles mainly originate from the large number of automotive vehicles and consequent increase of emissions in urban areas. Fine particles are those with diameters smaller than 2.5 μm, while the ultrafine particles have a diameter smaller than 0.1 μm [20]. A significant portion of these very small particles is composed of sulfates and nitrates, and can also include hydrocarbons, benzene, toluene, metals and other substances in their adsorbed molecules [21].

Studies have been conducted to identify how fine and ultrafine particulate matter are formed and what are their chemical composition [22]. These particles can be formed in a primary way (through the burning of fossil fuels) and secondarily in the air by means of nucleation. This phenomenon has been linked to high concentration levels of SO_2. The sulfur, which is in fuels and lubricant oils, contributes in the formation of aqueous aerosol particles that ultimately become part of the fine and ultrafine particulate material [22]. In recent decades, patho-physiologic studies on the action of various pollutants in the human body have been carried out.

High concentrations of oxidant and pro-oxidant agents in polluted air promote oxidative stress and inflammatory respiratory responses [23]. Of note, oxidative stress is a potentially harmful process that occurs when there is either an excess of free radicals or a decrease in antioxidant defense. The combination of both events may also occur [24]. Indeed, studies have linked air pollution to inflammatory oxidative processes [20,25–27]. Particulate matter (PM_{10}) affects the upper bronchi leading to pulmonary inflammation, while fine particles are transferred to the blood, potentially triggering a systemic inflammatory process [28]. Inhalation of these fine particles and their translocation to interstitium can cause an inflammatory response with subsequent release of pro-thrombotic factors and inflammatory cytokines into the blood circulation due to oxidative stress.

Oxidative stress activates specific transcription factors which include nuclear factor-K B, activator of protein-1, chemokines and other pro-inflammatory mediators [9]. It is assumed that the local pulmonary inflammation after exposure to air pollution is only the trigger for the systemic inflammatory reaction.

The fact that the tropospheric pollution triggers systemic inflammation is one of the relevant aspects that have recently been studied. Some studies with controlled exposure using fine concentrated ambient particles (CAPs) have shown alterations in systemic inflammation and biomarkers [29,30].

Thompson et al. [31], in a retrospective analysis using repeated-measures data, investigated the association between ambient air pollution and measurements of interleukin-6 (IL-6) and fibrinogen in 45 adults. In this study, exposure to ambient levels of O_3 and SO_2 was positively and significantly associated with increased levels of IL-6. This association demonstrated a cumulative lag effect with the strongest effects observed using 3- to 5-day moving averages.

Panasevich et al. [32] conducted a study aiming to investigate how long-term (years) and short-term (hours to days) air pollution exposure may affect the levels of some biomarkers for cardiovascular disease: IL-6, tumor necrosis factor-alpha (TNF-alpha), C-reactive protein (CRP), fibrinogen and plasminogen activator inhibitor-1 (PAI-1). This was a large population-based case–control study. It included 1536 first-time myocardial infarction patients aged 45–70 years from Stockholm, during 1992–1994. Controls were matched on age, gender and hospital catchment area. A significantly higher CRP and IL-6 levels was associated with long-term exposure (over 1, 5 and 30 years) to local traffic-related NO_2 and to residential heating-related SO_2. These results suggest that air pollution exposure may influence the serum levels of inflammatory biomarkers.

In other study, Calderón-Garcidueñas et al. [33] observed that healthy children who were exposed to high concentrations of air pollutants in Mexico City had their serum levels of inflammatory mediators, including TNF-alpha, prostaglandin (PG) E2, CRP, interleukin-1 beta, and endothelin-1, significantly increased when compared to children living in the city of Polototlán, where pollution levels were considerably lower than those in Mexico City. In 2009, Calderón-Garcidueñas et al. [34] reported that children who were exposed to high levels of $PM_{2,5}$ developed systemic inflammation and altered immune response. There was a significant correlation between cumulative concentrations of $PM_{2,5}$ and increased CRP and PGE2, confirming previous results that exposure to environmental pollution, particularly $PM_{2,5}$, leads to a systemic inflammatory process.

Therefore, it is possible to conclude that oxidative stress and inflammation induced by inhaled pollutants may lead to acute and chronic effects in the respiratory system, as well as contribute to a state of systemic inflammation. The worsening of air pollution has been associated to the increase of chronic inflammatory diseases (such as cardiovascular, neurodegenerative and auto-immune disorders), cancer and the worsening of previous inflammatory conditions [35,36].

3. May air contaminants influence the immune response and generate autoimmunity?

Epidemiological studies have also shown that the incidence of allergic diseases has increased partly because of the accumulating exposure to air pollutants [37,38]. Of note, tobacco smoke has been associated to negative effects on children's health [39,40]. Moreover, cigarette smoking has been associated with increases in the risk of autoimmune diseases [1]. In a recent review Arnson et al. [41] highlight the harmful effects of cigarette smoke on both humoral and cell-mediated immune responses.

Studies “in vitro” performed with culture of mononuclear cells exposed to extracts from cigarette smoke showed a negative effect on the production of inflammatory cytokines such as IL-1beta, IL-2, IFN-gamma and TNF-alpha [42,43]. However, other studies [44,45] could not demonstrate a reduction in the production of IFN-gamma (produced by TH1 cell) after polyclonal stimulation, in peripheral blood mononuclear cells of smokers in varying degrees. Nevertheless, Cozen et al. [45]

found out that for people who smoke over 20 cigarettes per day, the average level of IL13 and IL-5 (produced by TH2 cell) was respectively 146% higher than the one observed in nonsmokers, and 166% higher than the one observed in smokers of less than 20 cigarettes per day.

Additionally, exposure to silica is toxic on macrophages [46–48] and can induce apoptosis and exposure of intracellular self-antigens [49]. Experimental studies in which mice were exposed to silica have shown an increase in the production of autoantibodies, immune complexes [50,51] and number of B lymphocytes and CD4 T cells [52]. In an experimental study in which *New Zealand mixed* mice were exposed to silica, it was observed that serum levels of TNF-alpha increased significantly (1.5-fold) in their bronchoalveolar lavage when compared to mice which were administered saline in the airways. A six fold higher number of B lymphocytes compared with control group, and a considerable rise on the number of CD4+ T cells in superficial lymph nodes of mice which were exposed to silica were found. As there was not a significant increase in the number of regulatory T cell, there was an imbalance on ratio of regulatory T cells to T helper cells from 1:5 to 1:8 following silica exposure [52].

Pfau et al. [53] developed an experimental study, in order to test the hypothesis that asbestos could lead to a specific pattern of autoantibodies. C57BL/6 female mice were instilled into the trachea with amphibole asbestos (tremolite), wollastonite (a non-fibrogenic control fiber) or saline alone. The mice were observed during a period of 26-weeks. The group instilled with asbestos had a significantly higher frequency of anti-nuclear antibodies compared to the other two groups. The test also reported positive for antibodies to dsDNA and 52 kDa SSA/Ro. Interestingly, the group instilled with asbestos showed a deposit of immune-complexes in the kidney with a presence of glomerulonephritis. This study shows that inhalation of asbestos can trigger autoimmunity in mice.

In other experimental study, the presence of pro-TH1 and pro-TH2 chemokines was evaluated in nonatopic donors' PBMCs (peripheral blood mononuclear cells) incubated with diesel exhaust particle-polyaromatic hydrocarbons. The study showed that the functional effects of these chemokines resulted in an enhanced chemotaxis of TH2 cells [54]. Truly, TH2 lymphocytes have some functions: to produce interleukins (4,5,6,10,13) and to stimulate B cells, and consequently to raise the production of antibodies.

In another clinical study, Tebow et al. [55] found that children whose parents had smoked from birth to 11 years of a child's life were in lower quartile of production of INF-gamma compared to children whose parents were nonsmokers. Leonardi et al. [56] also conducted a cross-sectional study from 17 cities of Central European countries (Bulgaria, Czech Republic, Hungary, Poland, Romania and Slovakia) in pediatric population. They demonstrated an increase in the numbers of B lymphocytes, CD4 T cells, cytotoxic T lymphocytes (CD8 T cells) and natural killer cell (NK) associated to exposure to increase concentrations of PM_{25}. This analysis was adjusted for age, gender, passive smoking and recent respiratory illness. In that sense, Calderon-Garcidueñas et al. [34] reported a significant decrease in the number of NK cells and in the concentration of IFN-gamma in children living in Mexico City. Additionally, they also observed a significant increase in the number of activated CD4 T cells, CD14 cells, CD8T cells and B lymphocytes, associated with prolonged exposure to high concentrations of $PM_{2,5}$.

Fig. 1 illustrates a possible mechanism of the tropospheric pollution inducing inflammatory response and autoimmunity.

4. Air pollution and rheumatic diseases

Recently, Selmi [57] found out, after a PubMed query (2008–2009), that there was an immense result discrepancy in the search when the term “autoimmunity” was used isolated or as “autoimmunity and epidemiology”. When “autoimmunity” was typed, the results corresponded to 3455 publications. However, when the authors searched the terms “autoimmunity and epidemiology” they found only 266 publications. These results illustrate the small number of epidemiological studies which investigate autoimmunity. In recent years, studies using geo-epidemiology models started evaluating the environmental influences on susceptibility to autoimmune diseases [58–62]. However there were few research works studying the influence of air pollution and its effects on autoimmunity.

Studies evaluating the effects of inhaled pollutants on rheumatic diseases started with the investigation of occupational exposure. Only in the last decade tropospheric pollution began to be linked to rheumatic diseases. Our review focused on studies of inhaled pollutants in rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), systemic lupus erythematosus (SLE), scleroderma, inflammatory myopathies, primary vasculitis and spondyloarthropathies. Sixty-five articles were selected for this review's section: 14 on randomized controlled trial/meta-analysis/cohort studies, 48 on well-designed case control study/nonrandomized clinical trial/case reports and four on consensus/expert opinion/reviews.

4.1. Rheumatoid arthritis and juvenile idiopathic arthritis

Studies performed with identical twins have shown that genetics and environmental factors contribute to the onset of RA [63–65]. These studies, involving environmental factors and RA, are able to assess the influence of smoking and occupational exposure to silica.

Tobacco smoke from cigarettes, cigars and pipes is composed by more than 4500 different toxic substances, including carbon monoxide (CO), nicotine, tar, formaldehyde, hydrogen cyanide and tetrachlorodibenzo-p-dioxin (TCDD). Some studies have shown an association between exposure to cigarette smoke in adults and a higher risk of developing RA [1,41,65–68].

In 2005, Jaakkola and Gissler [69] evaluated 58,841 newborns in order to verify the influence of maternal smoking during pregnancy and the risk of developing chronic inflammatory polyarthropathies, especially JIA in the first seven years of life. They found a rate of chronic inflammatory polyarthropathies and JIA twice and three times higher respectively in children whose mothers smoked more than 10 cigarettes per day during pregnancy, although the effect was limited to baby girls.

Other recent studies have shown that there is an interaction between genetic factors and smoking in the development of RA, especially among seropositive RA patients [70–73].

In a case–control study, Karlson et al. [74] evaluated the interaction between HLA-SE and smoking in 439 RA Caucasian women and controls. Exposure to tobacco smoke was categorized as never versus ever smoking, and pack-years of smoking dichotomized as light smoking or never versus heavy smoking ($\leq$10 and $\geq$10 pack-years, respectively). They observed a significant interaction between the HLA-DRB1 shared epitope and heavy cigarette smoking. The observed interaction between HLA-SE and smoking was strongest for seropositive RA. These results suggest that it is important to consider smoking's cumulative dose when evaluating gene–environmental interaction in RA. In addition, in a recent meta-analysis study, Sugiyama et al. [75] assessed 16 studies selected from a total of 433. They demonstrated that the risk of developing RA was about twice and 1.3 times greater for male smokers and female smokers, respectively, compared to nonsmokers.

Moreover, occupational exposure to inhaled pollutants such as silica can cause chronic lung inflammation and it has also been reported as a possible risk factor for the development of autoimmune diseases. Over the past 45 years, studies have shown a connection between workers who have been exposed to silica and the development of autoimmunity and connective tissue diseases such as RA [76–79] and SLE [80–83].

Crystal silica is an abundant mineral found in rocks, sand and soil. It can also be found in the atmosphere, as fractions of small particles, hence crystalline silica can be inhaled [36]. Inhaled silica particles activate macrophages, stimulating the secretion of pro-inflammatory cytokines [46]. There is evidence that silica has an adjuvant effect on antibody production [47,49,50]. It has also been suggested that silica

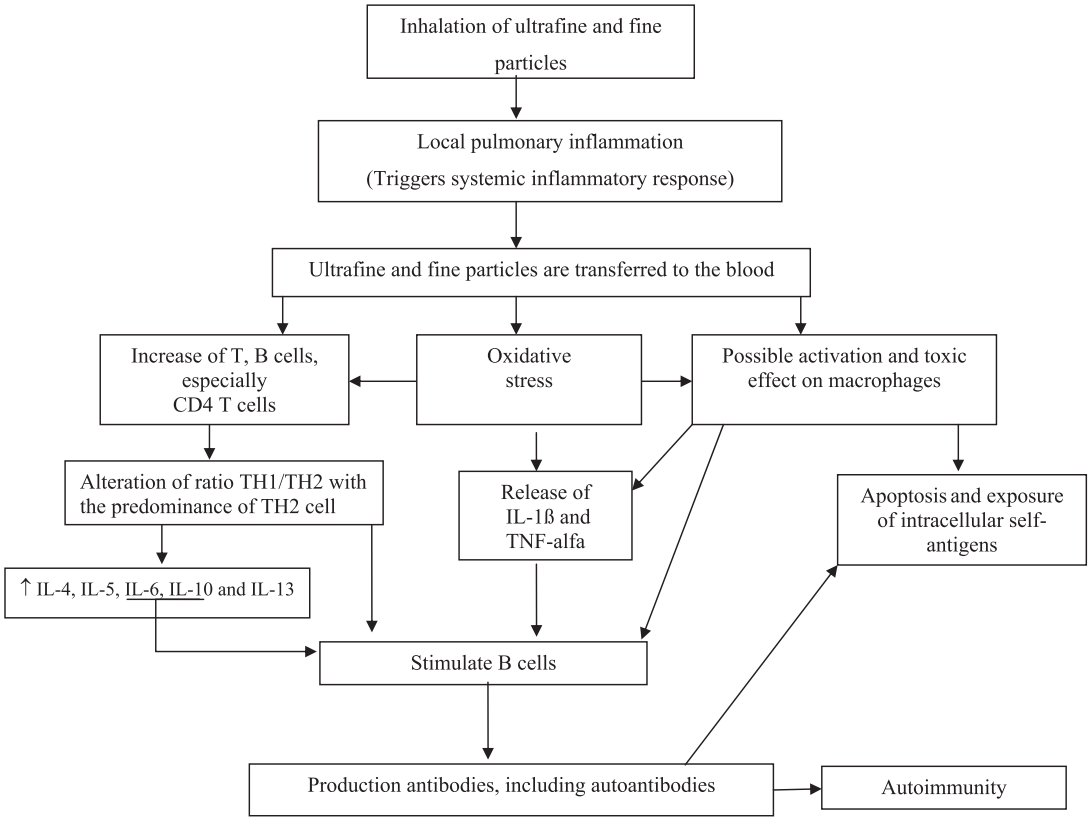

Fig. 1. Tropospheric pollution inducing inflammatory response and autoimmunity: a possible mechanism.

can activate the immune system by releasing "reactive oxygen species". Therefore, silica exposure may predispose or precipitate the development of connective tissue diseases, such as RA [84,85]. Stolt et al. [86], in another case–control study conducted in Sweden (part of the "Epidemiological Investigation of Rheumatoid Arthritis — EIRA"), investigated 276 men 18–70 years old exposed to mineral dust, such as silica, due to occupational or recreational contact. Men exposed to silica were more susceptible in developing RA, with an odds ratio of 2.2 (95% CI 1.2 to 3.9) in men aged 18 to 70 years and an odds ratio of 2.7 (95% CI 1.2–5.8) in men aged 50 to 70 years. This analysis was adjusted according to age, smoking habits and location.

Olson et al. [85] assessed 235 adult patients with onset of symptoms or recent RA diagnosis and 725 controls. They were evaluated by means of questionnaires regarding occupational history. The authors reported that inhaled particles were associated to RA, mainly amid men and that exposure to mineral dust and body vibration had a dose–response relation.

Recent evidence has shown an association between tropospheric pollution and RA, likewise in JIA. In a prospective cohort study, Hart et al. [87] assessed the risk of incidence of RA in adult women in relation to the distance these women lived from highways in the USA. Data analysis was adjusted for age, race, annual calendar, parity, lactation, menopause, use of hormonal reposition, contraceptive use, body mass index, physical activity and smoking. The authors observed a high risk of RA (RR = 1.31, 95% CI 0.98–1.74) in women who lived within a radius of 50 m from the highways in comparison to women who lived more than 200 m away from the highways.

Zeft et al. [88], in a study conducted in Utah, USA, evaluated the association between concentrations of fine particulate matter in the air and the onset of symptoms of 338 children diagnosed with JIA, between 1993 and 2006. It was observed that a high risk of JIA onset in children under five years associated with higher concentrations of $PM_{2,5}$ and stagnant air conditions in the preceding 14 days (RR = 1.60, 95% CI 1.00–2.54).

4.2. Systemic lupus erythematosus

Experimental and epidemiological studies have linked occupational exposure to silica [80–82,88–91], pesticides [92,93], solvents [83,91,93], and other inhaled substances to the development of SLE.

Two cohort studies evaluated occupational exposure to silica. Sanchez-Roman et al. [94] observed high rates of SLE in 50 workers who were exposed to silica in a powder factory for about six years when compared to the estimated rate of SLE in the general population. In another study, Conrad et al. [95] also found high rates of SLE in silica-exposed workers in uranium mines.

Parks et al. [90] conducted a population-based case–control study to evaluate the association between occupational exposure to silica and SLE in the southwestern of United States. The authors evaluated 265 patients with diagnoses of SLE and 355 controls matched by age, gender and state of residence. In this study, an association between exposure to silica dust and the development of SLE was observed, and this association was stronger in groups with medium- or high-level of silica exposure.

There are controversies as far as the tobacco smoke and SLE development are concerned, despite the fact that several studies have demonstrated a positive association between SLE and smoke. In a large retrospective analysis, Freemer et al. [96] found higher levels of dsDNA in current smokers if compared to never-smokers. Ghaussy et al. [97] studied the correlation of smoking status with disease activity (SLEDAI score) and cumulative organ damage (SLICC/ACR-DI). The authors showed that the SLEDAI score was significantly higher in current smokers compared to former smokers and never-smokers, but no significant difference was observed in SLICC/ACR scores. In a meta-analysis study, Costenbader et al. [98] demonstrated a small increase in the risk of SLE development by current smoking; however they did not show the same risk in past smoking.

In a recent study, Simard et al. [99] assessed the exposure to cigarette smoke in early life associated with the incidence of SLE in

adult women. The data analysis was adjusted according to race, birth weight, prematurity and parents' occupation. An increased risk of SLE incidence was absent in women whose parents smoked during pregnancy. The study did not find an association with exposure to cigarette smoke during childhood either. Kiyohara et al. [100] evaluated 152 Japanese women with SLE and 427 health controls aiming to investigate the relationship between N-acetyltransferase 2 polymorphism (responsible for the detoxification of aromatic amines by acetylation) with the SLE risk. Cigarette smoking was associated with an increase in the risk of SLE, and when the genotype of the population was assessed, it showed a three-fold higher risk of SLE in the slow acetylator genotype's women smoker.

As observed in RA, there are few studies evaluating air pollution and SLE development. In one of them, Dahlgren et al. [101] assessed an apparent cluster of cases of SLE in residents of a six-block area in Hobbs, New Mexico, where there was an excess of SLE cases when compared to the rest of the population. The locality with the highest number of cases was built on land that was an active oilfield from 1927 until the late 1960s. Pristane (an organic compost used as a lubricant, as an anticorrosion agent) was found in house dust at higher levels in homes investigated, likewise high levels of mercury in the air. The prevalence of SLE (OR = 19:33, 95% CI = 1.96–190.72) was higher than the one observed in the unexposed population.

Bernatsky et al. [102] evaluated the association between $PM_{2,5}$ and annual SLEDAI-2K score. Authors assessed 237 patients with lupus (mean age at the first visit was 41.2 years) who were followed up from 2000 to 2007. The total SLEDAI-2K scores were not associated with $PM_{2.5}$ levels, however anti-dsDNA was significantly associated with $PM_{2.5}$ levels of 24 h–48 h before the visits [OR relative to an increase in $PM_{2.5}$ of 10 μg/m^3 = 1.26 (95% CI, 0.96–1.65)]. The same effect was observed for the presence of renal casts [OR relative to an increase in $PM_{2.5}$ of 10 μg/m^3 = 1.43 (95% CI, 1.05–1.95)]. These results suggest that short-term variations in particulate matter's levels may trigger acute exacerbation in this autoimmune rheumatic disease.

4.3. Scleroderma

Although case reports provide weak evidence to determine an association between inhaled substances and scleroderma there are many studies linking exposure to inhalation of chemical solvents (like toluene and benzene) and herbicides (containing aminotriazole, bromouracil and diuron) to connective tissue diseases like scleroderma [103–105]. Prolonged trichloroethylene exposure has been linked to development of scleroderma, eosinophilic fasciitis and scleroderma-like disease [103,106].

Although epidemiological studies [103,107–110] have reported an association between systemic sclerosis and occupational exposure to silica, a possible association remains unclear as there are no rigorous studies assessing the risk of systemic sclerosis and the available studies show inconsistent results.

McCormic et al. [111] conducted a meta-analysis study. Sixteen studies were included in the analysis: nine case–control studies, three cohort studies and four with other designs. After statistical work, the Combined Estimator of Relative Risk (CERR) with 95% confidence interval (CI) was calculated for each one of the studies. The results suggested that exposure to silica is associated to an increased risk of developing scleroderma mainly among men. Nevertheless, the data were not enough to conclude that silica is a causal factor for systemic sclerosis.

4.4. Inflammatory myopathies

There are few studies evaluating the association of environmental factors and inflammatory myopathies. Some studies show that there is some seasonality with the onset of myopathies' symptoms in the spring [112,113] and summer [114–116]. Sarkar et al. [117] in order to assess possible seasonal patterns in the onset of polymyositis (PM) and dermatomyositis (DM), carried out a cross-sectional retrospective study of the time of onset of myositis in 503 patients from referral centers located in the USA. The authors did not find significant seasonal patterns of myositis onset in patients as a whole of PM or DM populations. However, in the antisynthetase-positive men patients, there was a difference in seasonality (peaked in March–April) when compared to the 122 female patients with these antibodies.

Further, Vegosen et al. [118] evaluated the conditions of birth of patients with idiopathic inflammatory myopathy to verify the influence of seasonal early environmental exposure in the later development of autoimmune diseases. This study evaluated two large groups: one included 307 patients with juvenile-onset inflammatory myopathy and 3942 healthy controls born between 1970 and 1999. Another group was composed of 668 adult-onset patients and 6991 controls born between 1903 and 1982. It was observed that for certain groups of juvenile inflammatory myositis, the distribution of births showed stronger seasonal effect than in the adult group, suggesting that perinatal environmental exposure may influence the onset of disease in childhood.

These findings suggest that environmental agents may act upon different genetic background, however more studies are needed in order to identify these agents and to set the time of prior exposure that is required to trigger the onset of symptoms.

4.5. Primary vasculitis

The primary small vessel vasculitis (Wegener's granulomatosis, microscopic polyangiitis and Churg–Strauss syndrome) has the presence of anti-neutrophil cytoplasmic antibodies (ANCA) as their markers. Interestingly, case reports, case series and case–control studies have shown an association between exposure to silica and vasculitis associated with ANCA [119–123].

Some epidemiological studies suggest that silica has some implication on the etiology of vasculitis associated with ANCA [123–125]. Bartúňková et al. [126], in order to assess an association between ANCA positive test and silica exposure, evaluated a group of 86 men who were exposed to silica dust for at least five years. This study was the first that compared ANCA status amid subjects' groups with different health effects of exposure to silica (simple pulmonary silicosis, complicated pulmonary silicosis and without pulmonary silicosis) and non-exposed control group. Higher ANCA positivity test was found only in the groups of patients with pneumoconiosis (simple or complicated). Silica exposure alone, however, without typical silicosis, was not associated with ANCA positive test.

4.6. Spondyloarthropathy

The knowledge on the exact etiology and pathogenesis of spondyloarthropathies has not yet been fully understood, although there is some evidence showing the importance of genetic background on susceptibility to these diseases and the importance of unidentified environmental factors that lead to release of inflammatory cytokines such as TNF-alpha [58]. Gastrointestinal infections have been shown as being the trigger of spondyloarthritides, but so far, no environmental factor, including tropospheric pollution, was clearly associated to spondyloarthropathies.

Table 1 includes the studies of inhaled pollutants or chemicals in rheumatic autoimmune disease based on levels of evidence [127].

5. Conclusions

Previous studies involving air pollution and its effects on human health date from the first half of the XX century. The studies have indicated that the main adverse outcomes were on respiratory and

Table 1
Studies of inhaled pollutants or chemicals in rheumatic autoimmune disease based on levels of evidence.

Variables	Levels of evidence
Rheumatoid arthritis	
Cigarette smoking	A [69,71,75], B [65–68,72–74] and C [41,70]
Silica	A [77,78,84] and B [76,79,85,86]
Tropospheric pollutants	A [87] and B [88]
Systemic lupus erythematosus	
Cigarette smoking	A [98,99] and B [96,97,100]
Silica	A [82,94,95], B [80,81,83,90,91] and C [89]
Tropospheric pollutants	A [102]
Solvent/pristane/pesticides	B [83,91–93,101]
Systemic scleroderma	
Silica	A [111] and B [107–110]
Solvents/pesticides	B [103–106]
Primary vasculitis associated with ANCA	
Silica	B [119–126]

Level A — randomized controlled trial/meta-analysis/cohort studies; *level B* — well-designed case control study/nonrandomized clinical trial/case reports; *level C* — consensus/expert opinion.

cardiovascular systems [128–130]. Many of the harmful effects to human health caused by tropospheric pollutants have been linked to fine and ultrafine particles. These particles can be transferred to the blood system, potentially triggering an immune and inflammatory response.

The fact that tropospheric pollution triggers systemic inflammation is one of the relevant aspects that have been recently studied. This contributes to the knowledge on the adverse effects of air pollutants that are extended to the immune system and inflammatory cascade and can trigger and exacerbate many diseases such as systemic autoimmune ones.

Environmental factors contribute to the onset of autoimmune diseases, especially smoking and occupational exposure to silica in rheumatoid arthritis and systemic lupus erythematosus. Other diseases such as scleroderma may be triggered after exposure of inhalation of chemical solvents, herbicides and silica. Similar relationship has been shown between vasculitis associated with ANCA and silica. Very few studies showed that air pollutants may trigger or exacerbate juvenile idiopathic arthritis and systemic lupus erythematosus. In contrast, no studies of tropospheric pollution triggering inflammatory myopathies and spondyloarthropathies were carried out.

Therefore, air pollution is one of the environmental factors involved in systemic inflammation and autoimmunity. Further studies are needed in order to evaluate air pollutants and their potentially serious effects on autoimmune rheumatic diseases and the mechanisms involved in the onset and the exacerbation of these diseases.

Conflict-of-interest disclosure

The authors declare no competing financial interests.

Take-home messages

- Tropospheric pollution triggers systemic inflammation and this aspect has been studied recently.
- The fine and ultrafine particles can be transferred to the blood system, thus potentially triggering an immune and inflammatory response.
- Environmental factors contribute to the onset of autoimmune diseases, especially smoking and occupational exposure to silica in RA and SLE.
- Air pollutants have also been described triggering disease flare of juvenile idiopathic arthritis and systemic lupus erythematosus, respectively.

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Systemic Lupus Erythematosus, the genes and the anti-dsDNA: an explanation for different disease phenotypes

It has been demonstrated that anti–dsDNA autoantibodies can be present prior to clinical symptoms in patients with Systemic Lupus Erythematosus (SLE), and are implicated in the pathogenesis of lupus nephritis, a major cause of morbidity and mortality in SLE. Furthermore, these autoantibodies have been associated with decreased survival. However, their prevalence ranges from 40 to 60%, suggesting that exist two different types of SLE patients characterized by the presence/absence of anti-dsDNA antibodies. Recently, Chung et al. (**PLoS Genet. 2011 Mar;7(3):e1001323**) conducted a GWAS to identify genetic factors associated with anti–dsDNA autoantibody production,. They found that previously identified SLE susceptibility loci (STAT4, IRF5, ITGAM), and the major histocompatibility complex were strongly associated with anti–dsDNA positive SLE with far fewer and weaker associations observed for anti–dsDNA negative SLE. Furthermore, this was confirmed for other SLE susceptibility loci (BANK1, KIAA1542, and UBE2L3) that showed association with anti–dsDNA positive SLE but not associated with those anti–dsDNA negative.

All these data are of great impact because it really seems that is possible to divide the disease in two different clinical entities characterized by the presence of anti-dsDNA antibodies.

The strongest association signals were observed with MHC SNPs, most consistently with the HLA-DR2 and HLADR3 MHC serotypes. The HLA-DR3 association with SLE (tagSNP, rs2187668) was found to be far stronger in anti–dsDNA positive SLE as compared to anti–dsDNA negative SLE.

It is possible that these SNPs may favour the production of autoantibodies, resulting in a more “aggressive” disease. This result is in accord with those from other studies on different diseases such as Rheumatoid Arthritis. Here, the presence of anti-CCP antibodies is strongly associated with several genetic typical features such as the presence of SNPs in HLA-DRB1 (the shared epitope), PTPN22, PADI4, STAT4, and TRAF1/C5 loci. Improving the knowledge on the genetic of the disease and particularly on its implications with specific clinical features, can help in clarifying disease pathogenesis and could bring to the individual estimation of a genetic risk score.