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NOVEL HYPOTHESIS

Cadmium, one of the villains behind the curtain: has exposure to cadmium helped to pull the strings of seropositive rheumatoid arthritis pathogenesis all along?

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INTRODUCTION

Seropositive rheumatoid arthritis (RA) has been considered to be a stochastic process;[1] however, careful consideration of the natural history of RA and examination of some of the known environmental risk factors would suggest otherwise. Rather than a set of random initiating events, it is hypothesized here that there is an overarching etiological trigger factor to account for some of the known risk factors for disease development. The lung has been considered to be the initiating site of seropositive RA as a result of local rheumatoid factor and anti-citrullinated peptide (anti-CCP) antibody generation.[2] In this paper, it is hypothesized that inhalation of cadmium is an important etiological factor in seropositive RA development.

EVALUATION OF HYPOTHESIS

Natural history of both seropositive RA and cadmium exposure over the last 2 centuries

RA was first described in 1804 in Paris.[3] Given that such a unique disease was only described in the 19th century, coupled with the failure to demonstrate erosive RA in extensive studies of skeletal remains prior to the 19th century in Europe,[4] suggests that seropositive RA is triggered by a set of relatively contemporary environmental risk factors. The very low concordance of seropositive RA in monozygotic twins reinforces the concept that it is a disease influenced mainly by the environment.[5] Therefore, plausible environmental risk factors are likely to have emerged in the 19th century and peaked in the 1950s and 1960s at the height of the prevalence of seropositive RA.[6]

Cadmium is a heavy metal and is toxic to health at very low exposure levels and chronic exposure produces a wide variety of acute and chronic effects in humans.[7] The emission of cadmium over time has been measured using ultraclean procedures in snow and ice, measuring cadmium deposited at a high altitude, and therefore there is a record of potential exposure to cadmium in Western Europe dating back to before the industrial revolution.[8,9]

Prior to the industrial revolution cadmium emissions are thought to have been negligible, but increased sharply in the 19th century, peaking in the 1950s–1960s, a 15-fold increase from baseline.[8]

Relationship between increased cadmium exposure and smoking and the relationship between seropositive RA development and smoking

Cigarette smoking accounts for the development of 35% of all seropositive RA cases.[10] Compared to those individuals who had never smoked, the risk for former smokers was found to persist for as long as 20 years.[11] One study quantified the relative risk (RR) 15 years after smoking cessation to be 1.99 (95% CI: 1.23, 3.20) and very similar to the RR for current smokers of 2.24 (95% CI: 1.63, 3.07).[12] This would suggest the toxin within cigarettes responsible for seropositive RA development may remain within the body for up to 2 decades. Cigarette smoking is the most important source of cadmium in smokers[7] and the serum levels are raised significantly by three-fold in current smokers,[13] but the levels in former smokers return to 53% of those

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observed in comparable current smokers, less than 1 year after cessation.[14] However, cadmium tissue levels remain significantly elevated over 2 decades as a study demonstrated the mean cadmium lung concentrations of ex-smokers to only return to the baseline level of non-smokers after 21–22 years.[15] The progression of RA in terms of erosive disease is associated with current smoking rather than ex-smoking, with a Swedish study observing a clear-cut difference between current and former smokers and this finding interestingly was independent of anti-CCP positivity. This study did not record when the RA patients stopped smoking prior to their disease onset so it is difficult to determine if potentially raised levels of serum cadmium entering the diseased joint could conceivably play a part in RA disease progression.[16] It is conceivable that cadmium could play a part in both disease severity as previously suggested[17] and also in disease susceptibility as suggested here.

Occupations known to increase the risk of seropositive RA and their relationship with increased cadmium exposure

Some of the occupations associated with seropositive RA[18–21] are listed in Table 1. These seemingly unconnected and eclectic occupations are all associated with increased cadmium exposure.[22] Cement, mineral and hydraulic oils, plasterboard, asphalt, plastics, dyes, wood and diesel all have appreciable cadmium contents that can be inhaled in the workplace as dust or fumes.[23]

Seropositive RA risk factors (independent of cigarette smoking) include: lower socio-economic class, a low level of a formal education, residing close to main roads and living in the north-east of the US and are all associated with increased cadmium exposure.

The studies observing an association between the environmental risk factors listed above and seropositive RA have been reviewed.[24] Low socio-economic class and a low level of a formal education have been consistently found to be strongly associated with RA independent of cigarette smoking[24] and are also strongly associated with increased cadmium exposure independent of cigarette smoking.[25] Cadmium levels at the roadside are increased by 35% and return to normal within 100 m of the roadside.[26] Cadmium is contained very locally by the roadside within dust[27] and a Turkish study observed increased hair levels of cadmium in children attending schools in close proximity to vehicle traffic.[28] This is obviously an extremely localized phenomenon and it is interesting to note a reported increased risk of 30% of RA in those women living within 50 m of a major road compared with women living only 200 m away.[29] Recently this finding was confirmed with an increased RA incidence with proximity to traffic, with an odds ratio of 1.37 (95% CI: 1.11, 1.68) for residence $\leq$ 50 m from a highway compared with residence $>$ 150 m away.[30] This finding is not explained by industrial pollution *per se* as two studies found no consistent association between air pollution and an increased RA risk.[31,32] Carroll investigated the mean concentration of cadmium in the air of 28 US cities and demonstrated a marked correlation with mortality rates from hypertension and coronary heart disease.[33] Interestingly in this study, indexes of air pollution did not correlate with mortality from hypertension and coronary heart disease, suggesting that air levels of cadmium are not necessarily associated with increased air pollution. Residing in the north-east of the US is associated with the highest cadmium exposure compared to the other regions of the US[22] and this correlates with an increased incidence of RA in the same region of the US.[34,35]

Cadmium levels in RA

The first study of serum cadmium levels in RA observed similar levels to controls and RA synovial fluid cadmium to be low compared to levels in cadavers.[36] More

Table 1 Overview of the reported occupations associated with RA and also associated with increased cadmium exposure

Occupations associated with seropositive RA	Gender	Odds ratio (OR)/relative risk (RR) 95% confidence interval (CI)
Rubber and plastic workers	Female	OR: 2.9, 95% CI: 1.1–7.4[18]
Smelters and metal foundry workers	Male	OR: 2.8, 95% CI: 1.0–7.4[18]
Bricklayers and concrete workers	Male	OR: 2.6, 95% CI: 1.3–4.9[18]
Electrical and electronics workers	Male	OR: 1.8, 95% CI: 1.0–3.1[18]
Work exposure to mineral oil	Male	RR: 1.4, 95% CI: 1.0–2.02[19]
Work exposure to hydraulic oil	Male	RR: 1.7, 95% CI: 1.1–2.6[19]
Asphalters	Male	OR: 14.0, 95% CI 1.2–799.0[20]
Printmakers and process engravers	Female	OR: 5.5, 95% CI 0.9–32.6[21]
Conductors, freight and transport workers	Male	OR: 4.7, 95% CI 1.4–16.3[21]

recently Afredi *et al.* have demonstrated that the concentrations of cadmium are significantly higher in blood, urine and scalp hair of smoking and non-smoking RA patients.[37,38]

Potential role of cadmium in the induction of anti-CCP antibody production

Cadmium exists as a nanoparticle in cigarette smoke and also in the fumes and dust associated with the occupations listed in Table 1.[22] Recent research has identified that a number of nanoparticles, including silica, can induce lung citrullination via activation of cellular calcium channels with a subsequent rise in intracellular calcium and activation of peptidyl arginine deiminase and subsequent peptide citrullination.[39] This important research, therefore, links the known association between exposure to silica dust and the development of seropositive, as opposed to seronegative, RA[40] Likewise, cadmium has the potential to cause citrullination as cadmium is a potent activator of calcium channels and significantly raises intracellular calcium levels.[41,42]

SUMMARY

Exposure to cadmium links smoking, the most important etiological factor in the development of seropositive RA, and many of the other known contemporary risk factors. Epidemiological studies investigating the link between smoking, occupations, social class, region of residency and RA should consider cadmium exposure as an important confounding factor. Studies to determine if cadmium can induce citrullination will be pivotal in determining if cadmium has indeed been the villain behind the curtain regarding the pathogenesis of seropositive RA.

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