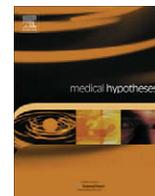




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A role for the body burden of aluminium in vaccine-associated macrophagic myofasciitis and chronic fatigue syndrome

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SUMMARY

Macrophagic myofasciitis and chronic fatigue syndrome are severely disabling conditions which may be caused by adverse reactions to aluminium-containing adjuvants in vaccines. While a little is known of disease aetiology both conditions are characterised by an aberrant immune response, have a number of prominent symptoms in common and are coincident in many individuals. Herein, we have described a case of vaccine-associated chronic fatigue syndrome and macrophagic myofasciitis in an individual demonstrating aluminium overload. This is the first report linking the latter with either of these two conditions and the possibility is considered that the coincident aluminium overload contributed significantly to the severity of these conditions in this individual. This case has highlighted potential dangers associated with aluminium-containing adjuvants and we have elucidated a possible mechanism whereby vaccination involving aluminium-containing adjuvants could trigger the cascade of immunological events which are associated with autoimmune conditions including chronic fatigue syndrome and macrophagic myofasciitis.

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Introduction

Macrophagic myofasciitis (MMF) is a recently described histopathological lesion which is mainly, though not exclusively, diagnosed in adult patients [1–3]. Clinical manifestations of MMF include diffuse myalgia, arthralgia, chronic fatigue and muscle weakness. The prevalence in patients of musculoskeletal pain and chronic fatigue of duration in excess of six months is approximately 88% and 93%, respectively [2]. Fatigue is disabling in 87% and affects patient's physical and mental functioning in 53% of cases [4]. The 1994 CDC and 1991 Oxford criteria for chronic fatigue syndrome (CFS) are fulfilled in 47% and 40% of patients, respectively [4]. The pathology of MMF is characterised by pathognomonic focal epi-, peri- and endo-mysial infiltration of large periodic acid-schiff (PAS)-positive macrophages, intermingled with CD8⁺ T-cells, in the absence of conspicuous muscle fibre damage [1,2]. Electron microscopy reveals the presence of a crystalline material in the cytoplasm of macrophages which is identified as a form of aluminium hydroxide which is used as an adjuvant in vaccines to stimulate the immune response [5]. MMF is found to be concomitant with the long term persistence of aluminium hydroxide at the site of a previous intramuscular injection [5], with the time between immunisation with aluminium adju-

vant (vaccine) and onset of symptoms and muscle biopsy ranging from 3 months to 10 years [2,6]. The low detection rate of MMF in individuals who are exposed to aluminium-based adjuvants in vaccines and have undergone deltoid muscle biopsies prompted the WHO to propose the working hypothesis that MMF occurred in a predisposed subset of individuals who shared an impaired ability to clear aluminium from their muscle [7]. While there are data which suggest genetic predisposition to MMF [8–10], for example, in relation to autoimmune disease [11], the WHO's subset of individuals remains to be identified and there are no definitive data concerning the clearance or persistence of aluminium in human muscle tissue. However, the pathology of MMF is reproduced in animal models [12,13] and there is preliminary evidence of a role for genetically determined factors related to the immune cascade in MMF in rats [13].

The relationship between the myriad symptoms which are associated with a diagnosis of MMF and the muscle pathology is uncertain as is the role of aluminium in disease aetiology. It is, for example, unknown if MMF is a manifestation of another underlying condition or if it is the cause or source of the associated symptoms. CFS is a relatively common disease which, like MMF, can be severely disabling and is also of unknown aetiology [14]. It has also been linked with vaccination though whether or not aluminium adjuvants are involved in the aberrant immune response which is characteristic of CFS is equivocal [15]. There are already strong links between MMF and CFS and we have formed the

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opinion that these conditions might be exacerbated by an increased sensitivity to exposure to aluminium with the latter also being recognised as an elevated body burden of aluminium. Herein, in the first test of this hypothesis, we describe the first case of MMF and CFS coincident with an increased body burden of aluminium.

Case report

A 43-year-old man with no history of previous illness presented in October 2003 with symptoms suggestive of viral illness and lethargy. Symptoms progressed during the following weeks to additionally include vertigo, anxiety, feeling clumsy and low mood. Routine blood tests including glandular fever serology were normal. The patient was referred to neurology following the appearance of left-sided diplopia, leaning to the left side and impaired sensation on the left. In January 2004, a neurological examination including MRI showed nothing unusual and the patient was diagnosed with post viral syndrome with associated depression and anxiety. The patient was prescribed anti-depressants following which he developed cognitive impairment, slowness of speech and short term memory loss. He was referred to a psychologist. The anti-depressants were discontinued in early 2006 as they were deemed by the patient to be of no benefit. In March 2004, the patient asked if his condition might be associated with vaccinations administered between 30th April and 28th May 2003 for hepatitis A, hepatitis B, polio and tetanus/diphtheria. In September 2004, the patient was referred to an immunologist who diagnosed chronic fatigue syndrome with no trigger identified. In December 2004, the patient completed an adverse drug reaction form in relation to hepatitis vaccination and in August 2007 an industrial injuries tribunal concluded that the patient suffered from impaired psychological and muscular function and awarded him 50% disability and cited the aforementioned series of vaccinations as the cause of the injury. In March 2005, the patient was diagnosed with type 2 diabetes mellitus, diet controlled and hyperlipidaemia and, in respect of the latter, undertook a course of simvastatin which was changed to a fibrate in November 2006 due to poor tolerance of the statin. A second neurology appointment in January 2006 which included MRI showed no unusual neurophysiology. In June 2006, the patient was referred to the Centre de Référence des Maladies Neuro-Musculaires in Créteil, Paris where a muscle biopsy was used to diagnose macrophagic myofasciitis (MMF). An open left deltoid muscle biopsy was performed. Muscle samples were conventionally processed for light microscopy using standard procedures. Frozen and paraffin-embedded sections were stained using haematoxylin-eosin (H&E), Masson and modified Gomori trichromes, Sudan black, Morin stain and periodic acid-schiff (PAS) while histoenzymatic reactions which included NADH-tetrazolium reductase, succinate dehydrogenase, cytochrome C oxidase, myophosphorylase, and phosphofructokinase were also performed. Expression of major histocompatibility complex (MHC)-1 (HLA-ABC), CD3, CD8 and CD56/neural cell adhesion molecule (NCAM) (Novocastra, UK) were evaluated by immunoperoxidase assay performed on frozen sections using a Ventana® automated immunostainer (Tucson, Az).

Examination by light microscopy disclosed focal inflammatory infiltrates, localized in both epimysium and perifascicular endomysium (Fig. 1). Infiltrates were made of cohesive large macrophages, which did not form multinucleated giant cells and were intermingled with lymphocytes, mainly CD8⁺ T-cells. Macrophages had strongly PAS-positive, finely grained cytoplasmic content and were markedly fluorescent with morin stain, demonstrating the presence of aluminium hydroxide within cells. Myofibre changes were limited to rounded atrophy of fibres hemmed by macrophagic infiltrates. The diagnosis of MMF which has been linked

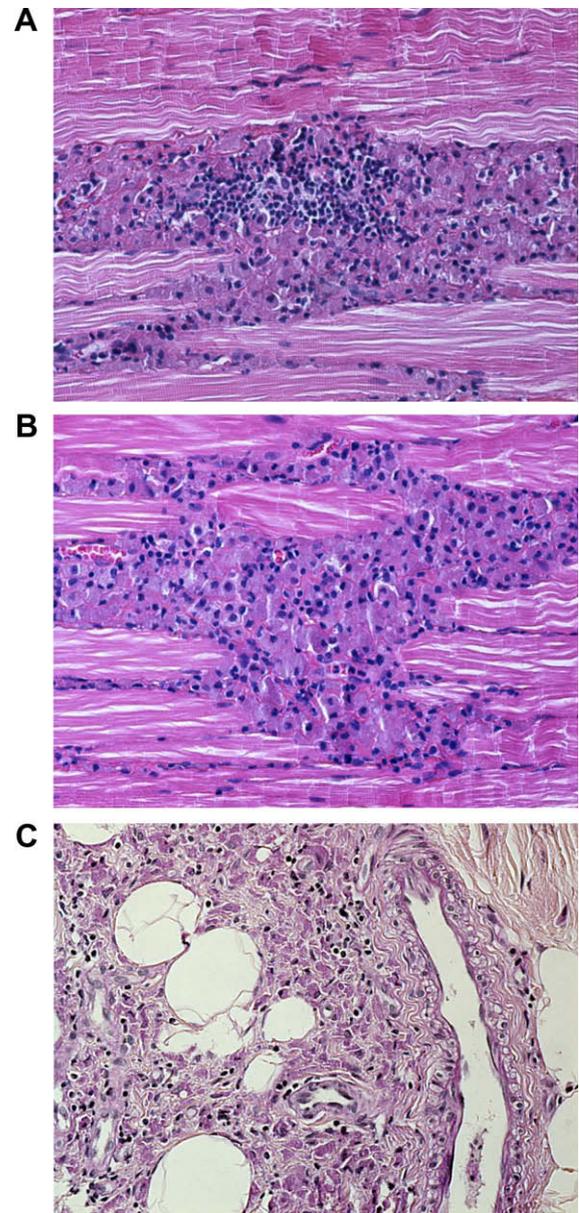


Fig. 1. Deltoid muscle biopsy: light microscopy examination. Focal infiltrates within endomysium (A, B) and epimysium (C) made of large basophilic mononucleated macrophages intermingled with lymphocytes (A: paraffin sections; B: hematoxylin-eosin; C: periodic acid-schiff [PAS]). Macrophages appear strongly PAS-positive (C).

to the use of aluminium-based adjuvants in vaccines was supported by the fact that each of the five vaccinations received by the patient in April/May 2003 included an aluminium-based adjuvant.

In May 2007, an estimate of the patient's body burden of aluminium was obtained from the analysis of five consecutive 24 h urine samples (Table 1). Total aluminium and creatinine were measured using established methods [16]. Both the patient's creatinine-normalised (mean = 92 ± 25 nmols/mmol) and 24 h excretion (mean = 1181 ± 232 nmols/24 h) of aluminium were significantly higher than expected for a normal male of the same age [16]. The data suggested that the patient had a higher than expected body burden of aluminium. This was supported by a further set of urine analyses in July 2007 (Table 2). During the five consecutive days over which 24 h urine samples were collected the patient was asked to include up to 1.5 L of a silicon-rich (ca

Table 1

Analyses of aluminium content of urine over five consecutive days.

Sample indenty	Urine 24 h (Vol mL)	[Creatinine] (mmol/L)	Urine [Al] (nmol/L)	[Al] nmol/mmol Creatinine	Al excreted in 24 h (nmoles)
1 (08/05/07)	2108	7.39	600	81	1265
2 (09/05/07)	2356	6.19	511	83	1204
3 (10/05/07)	2220	4.96	548	111	1217
4 (11/05/07)	1792	7.18	444	62	796
5 (12/05/07)	2192	5.17	648	125	1421
Mean (sd)	2134 (211)	6.18 (1.15)	550 (79)	92 (25)	1181 (232)

Table 2

Analyses of aluminium content of urine following drinking of 1.5 L of silicon-rich mineral water each day over five consecutive days.

Sample indenty	Urine 24 h (Vol mL)	[Creatinine] (mmol/L)	Urine [Al] (nmol/L)	[Al] nmol/mmol Creatinine	Al excreted in 24 h (nmoles)
1 (18/07/07)	1986	6.58	776	118	1541
2 (19/07/07)	2344	6.40	729	114	1709
3 (20/07/07)	1991	6.43	795	124	1583
4 (21/07/07)	2233	6.62	587	89	1311
5 (22/07/07)	2301	5.92	466	79	1073
Mean (SD)	2171 (171)	6.39 (0.28)	671 (140)	105 (20)	1443 (252)

Table 3

Analyses of aluminium content of urine over 5 consecutive days following drinking approximately 0.75 L of silicon-rich mineral water each day for 3 months.

Sample indenty	Urine 24 h (Vol mL)	[Creatinine] (mmol/L)	Urine [Al] (nmol/L)	[Al] nmol/mmol Creatinine	Al excreted in 24 h (nmoles)
1 (28/10/07)	1986	6.71	197	29	391
2 (29/10/07)	2508	6.13	194	32	487
3 (30/10/07)	2386	6.39	187	29	446
4 (31/10/07)	2272	7.50	147	20	334
5 (01/11/07)	1796	8.74	261	30	469
Mean (sd)	2190 (292)	7.09 (1.05)	197 (41)	28 (5)	425 (63)

600 $\mu\text{mol/L}$ as silicic acid) mineral water as part of their daily intake of fluids. Silicon-rich mineral waters have been shown to titrate aluminium from the body tissues and may, therefore, give a better overall approximation of the actual body burden of aluminium. While the 5 day volume of urine was unaffected by including the silicon-rich mineral water in the diet the 5 day excretion of aluminium increased significantly from 5903 to 7217 nmoles. These analyses confirmed that the patient had a higher than expected body burden of aluminium. The patient continued without prompting to drink approximately 0.75 L/day of the silicon-rich mineral water and at the end of October 2007 the measurement of aluminium in a further set of 24 h urine samples taken on five consecutive days revealed a significant reduction in his urinary excretion of aluminium from *ca.* 1400 nmoles/24 h to *ca.* 425 nmoles/24 h (Table 3). While this result suggested that the patient's body burden of aluminium was reduced during this period there was no noticeable concomitant improvement in his condition.

Discussion

This is the first report of the coincidence of macrophagic myofasciitis (MMF), chronic fatigue syndrome (CFS) and aluminium overload in an individual. While the initial diagnosis of CFS did not identify a disease trigger the condition developed progressively following five vaccinations over a period of four weeks. Each of these vaccinations included an aluminium-based adjuvant and, 3 years later, the persistence of aluminium salt at an injection site was confirmed by muscle biopsy in the diagnosis of MMF. Aluminium overload was diagnosed 4 years post vaccination though the provenance of this condition is unknown. Early indications are that the aluminium overload was, in the short term, successfully treated using regular drinking of a silicon-rich mineral water. MMF, CFS and aluminium overload have a number of symptoms which

are in common and most notably muscle weakness, muscle pain and chronic fatigue. The coincidence of MMF and CFS in this case has been attributed to a series of vaccinations which included aluminium-containing adjuvants though the attribution was made without reference to a specific mechanism or disease aetiology. Indeed, while there appears to be a burgeoning acceptance within the medical community that some individuals show an adverse reaction to vaccines which include an aluminium-based adjuvant the mechanism underlying such has not been elucidated [17,18]. In reviewing the case study presented herein and related information in the scientific literature we have provided a testable hypothesis for a mechanism of aluminium adjuvant-associated immunological disease.

The medical definition of the word 'adjuvant' is essentially; a substance used in conjunction with another to enhance its activity. Aluminium is clearly an effective adjuvant when used in vaccination and immunotherapy. It enhances the immune response to the antigen and to the allergen. While we have known about this property of aluminium for at least 80 years we still do not fully understand the mechanism which underlies its efficacy as an adjuvant [19]. Certainly aluminium salts do act as vehicles for the presentation of antigen/allergen though not only in the benign sense as they are also known to stimulate innate immunity in the absence of antigen [20] and, indeed, they have been shown to act as antigens themselves [21]. Thus aluminium is both adjuvant and antigen and this dual activity must raise questions about how the human body reacts to any exposure to aluminium. For example, when aluminium is used in vaccinations it is certainly acting as an adjuvant in that it enhances the immune response to the adsorbed antigen. In this way it ensures that when an individual has a future encounter with the antigen a rapid and effective immune response against the antigen is initiated. However, there is evidence that aluminium in adjuvants is also acting as an antigen

as a significant proportion of vaccine recipients retain a memory of their exposure to aluminium such that they show delayed hypersensitivity to subsequent exposures to aluminium [22,23]. Thus, vaccination and allergen therapies which incorporate aluminium-based adjuvants may sensitise recipients towards future exposures to aluminium. The manifestation of such an enhanced sensitivity to aluminium is probably as diverse as the myriad ways in which humans are exposed to aluminium in everyday life [24]. It may take the form of a skin reaction to topically applied antiperspirant or an allergic asthma triggered by aluminium in tobacco smoke. The response to a systemic aluminium challenge such as might be encountered following the injection of aluminium-based adjuvants used in vaccination and allergy therapy might be more severe and could begin to explain the myriad symptoms associated with conditions such as MMF [1], CFS [25] and, a related condition, cutaneous lymphoid hyperplasia (CLH) [26].

Sensitisation to aluminium may simply be one manifestation of the physiological response to biologically available aluminium. The biological availability of aluminium, as defined by its propensity to induce a biochemical response in an affected system, is known to depend upon the establishment over time of a threshold concentration or burden of aluminium [27]. The system, e.g. cell or tissue, copes with the burgeoning burden of aluminium up until a threshold concentration is reached which results in a net biochemical effect. While we do not understand fully how aluminium-based adjuvants work it could be assumed that their efficacy is based upon similar principles in that their injection into tissue results in a threshold concentration of aluminium being reached instantaneously. The actual site where the threshold is achieved might be the muscle fibre itself though more likely are the infiltrating and immunostimulatory macrophages, dendritic cells, monocytes or B lymphocytes [28,29]. The net biochemical effect of the resulting aluminium burden is the aforementioned dual activity of aluminium as both adjuvant and antigen. Since the establishment of threshold concentrations of biologically available aluminium will depend upon susceptible biochemical compartments, such as long-lived neurons, being exposed to aluminium over extended periods of time then for the majority of individuals the first exposure to such a burden is probably childhood vaccinations incorporating aluminium-based adjuvants. The immunological memory of these early exposures to biologically available aluminium may vary widely within the recipients such that thereafter there could be many different biochemical responses to a future exposure to aluminium. The nature of any such response would depend upon the level of the exposure and the extent to which a threshold concentration of aluminium was approached. In the case of future vaccinations involving aluminium-based adjuvants the latter would be achieved instantaneously at or close to the site of injection and in individuals who had retained a memory of their earlier exposure to aluminium could instigate a severe immune response with wide ranging health implications. The wider cascade of effects may involve the recruitment of aluminium antigens in other parts of the body or it may be mediated through other antigens which have been sensitised through their previous administration in conjunction with aluminium acting as an adjuvant. For example, recent research has demonstrated sensitisation to food allergens following their co-administration with aluminium salts such as antacid preparations [30].

Aluminium salts are the most effective adjuvants in use today and their widespread application over many decades is testimony to their success and, probably, to their safety. However, if their efficacy is based upon the mode of action which we have described herein, then a situation could occur when their use results in an anarchic immunological response and a cascade of unwanted health effects. Individual susceptibility to an adverse reaction may be dependent upon the combination of a previous sensitisation

to aluminium, for example, via childhood vaccination, and an ongoing aluminium overload. While the body may cope robustly with a mild but persistent immune response to aluminium overload the coping mechanism will be suddenly and dramatically overwhelmed by a new exposure to aluminium adjuvant. The latter, will not only enhance the antigenicity of itself but it will raise the level of the immune response against all significant body stores of aluminium. Under these conditions an individual's everyday exposure to aluminium will continue to fuel the response and myriad symptoms of associated autoimmunity will take over the life of the affected individual. The individual will now respond adversely to aluminium exposures which previously were not sufficient to elicit a biological response and the only solution will be to treat the aluminium overload and to reduce everyday exposure to aluminium. We are currently working on solutions to reduce the human body burden of aluminium [31] and one such solution has demonstrated some promise in the case which is the subject of this article. There is a requirement for a non-invasive method to both reduce the gastrointestinal absorption of aluminium and facilitate the excretion of systemic aluminium in the urine. We have known for some time that silicon is the natural antagonist to aluminium and acts to keep aluminium out of biota [32,33]. Recently we have shown that silicon-rich mineral waters can be used to reduce the body burden of aluminium in individuals with Alzheimer's disease [31]. In the case reported on herein we have demonstrated that regular drinking of a silicon-rich mineral water over a 3 month period dramatically reduced the body burden of aluminium from one which could be described as aluminium overload to a burden which might be considered as within the normal range. If this reduction persists with concomitant drinking of a silicon-rich mineral water we shall be interested to see if the health of the individual is improved over the long term.

Conclusion

We have described for the first time a case of vaccine-associated MMF and CFS which was coincident with an aluminium overload. We have shown that the latter might be addressed non-invasively by regular drinking of a silicon-rich mineral water. We have discussed this case in the light of a burgeoning acceptance that some individuals may be hypersensitive to aluminium-containing adjuvants in vaccines and we have suggested a possible mechanism of aluminium-induced immune disease. When it is considered that as many as 1% of recipients of aluminium-containing adjuvants may be sensitised to future exposures to aluminium then a cautionary case can be made in respect of future mass vaccinations (eg. against HPV) which include this form of adjuvant.

Conflicts of interest statement

We declare that we have no conflicts of interest.

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