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Chronic barium intoxication disrupts sulphated proteoglycan synthesis: a hypothesis for the origins of multiple sclerosis

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Summary High level contamination by natural and industrial sources of the alkali earth metal, barium (Ba) has been identified in the ecosystems/workplaces that are associated with high incidence clustering of multiple sclerosis (MS) and other neurodegenerative diseases such as the transmissible spongiform encephalopathies (TSEs) and amyotrophic lateral sclerosis (ALS). Analyses of ecosystems supporting the most renowned MS clusters in Saskatchewan, Sardinia, Massachusetts, Colorado, Guam, NE Scotland demonstrated consistently elevated levels of Ba in soils (mean: 1428 ppm) and vegetation (mean: 74 ppm) in relation to mean levels of 345 and 19 ppm recorded in MS-free regions adjoining. The high levels of Ba stemmed from local quarrying for Ba ores and/or use of Ba in paper/foundry/welding/textile/oil and gas well related industries, as well as from the use of Ba as an atmospheric aerosol spray for enhancing/refracting the signalling of radio/radar waves along military jet flight paths, missile test ranges, etc.

It is proposed that chronic contamination of the biosystem with the reactive types of Ba salts can initiate the pathogenesis of MS; due to the conjugation of Ba with free sulphate, which subsequently deprives the endogenous sulphated proteoglycan molecules (heparan sulfates) of their sulphate co partner, thereby disrupting synthesis of *S*-proteoglycans and their crucial role in the fibroblast growth factor (FGF) signalling which induces oligodendrocyte progenitors to maintain the growth and structural integrity of the myelin sheath. Loss of *S*-proteoglycan activity explains other key facets of MS pathogenesis; such as the aggregation of platelets and the proliferation of superoxide generated oxidative stress. Ba intoxications disturb the sodium–potassium ion pump – another key feature of the MS profile. The co-clustering of various neurodegenerative diseases in these Ba-contaminated ecosystems suggests that the pathogenesis of all of these diseases could pivot upon a common disruption of the sulphated proteoglycan-growth factor mediated signalling systems. Individual genetics dictates which specific disease emerges at the end of the day.

Introduction: the barium facts

Barium is a divalent alkali earth metal that is naturally present at elevated levels in certain soil types, oil/coal deposits and seawater [1,2]. Ba ores are exploited for many industrial, agricultural and medical applications [1,2]. The insoluble Ba sulphate is used as a suspension in contrast radiogra-

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phy in human and veterinary medicine, whilst the soluble Ba salts — acetate, sulphide, carbonate, chloride, hydroxide, nitrate — are highly toxic and used extensively by industry, the military and agriculture [3] for the manufacture of paper, pesticides, rubber, steel/metal alloys, welding rods, paints, fabrics, leather, fuel additives [4], TV/electronic components, bomb/gun explosives, flares, atmospheric aerosol sprays for refracting radar/radio waves, cloud seeding weather modification sprays, radar absorbing paints, ceramics, glazes, glues, soaps, depilatories, cements, bricks, drilling muds, dyes, inks, glass, water purifiers, magnets [1,2].

The distribution of MS clusters correlates with workplaces and environments that are associated with elevated levels of Ba

Occupational groups that have been identified as the highest risk for the development of MS, involve those involved in paper manufacturing, wood processing, leather, metal (especially zinc-related industries), welding, printing, textiles, electronics and agriculture [5—12]. Intriguingly, Ba salts are utilised as key ingredients in the fillers, glues, inks, pesticides, welding rods, etc., that are employed in *all* of these MS risk industries [1,2]. Furthermore, simultaneous exposure to the solvents that are also used in these industrial processes would exacerbate the problem of Ba exposure by increasing the permeability of the blood brain barrier [9], thereby enabling an increased uptake of Ba into the brain.

Some MS epidemiological studies have shown that examinations involving X-ray film exposure of the gastro intestinal tract represent a significant risk indicator for the development of MS [9,11]. Assuming that this observation represents more than mere coincidence, then the customary use of Ba sulphate in contrast radiography may represent the pertinent aetiological factor here, rather than the exposure to the actual X ray itself. In this respect, several studies have shown that toxic amounts of Ba can be absorbed across the gastro tract [1,2,13,14] following use of this supposedly insoluble compound in radiography, whilst other cases of Ba intoxication have resulted from the accidental use of the more soluble Ba carbonate compound [15] in radiography. Furthermore, It is likely that Ba would be absorbed considerably more efficiently across the 'leaky' gut membranes of those suffering from Crohn's or Ulcerative Colitis (IBS syndromes), and it is this class of patient who would represent a higher proportion of those being subjected to this type of exploratory radiography. On the other hand, the association between X ray examinations of the gastro tract and MS development could be more to do with the fact that both MS and IBS sufferers share the same genetic predisposition that determines susceptibility to both IBS and MS [16]; thereby discounting the possibility of an association between the aetiology of MS and Ba use in radiology.

The highest prevalence of MS has traditionally blighted the subsistent, rural populations scattered across the Northern hemisphere; e.g. in Saskatchewan, Nova Scotia, Iceland, Orkney island, North Eastern Scotland, N Ireland, Norway, Sweden, Finland [9,12,17], whilst, more recently, high incidence MS foci have started to emerge nearer to the equator in countries like Sardinia [18]. It is interesting that the soil types of these localities involve the limestones of Saskatchewan/Nova Scotia, the pre cambrian granites, basalts, mica schists of Iceland/Faroes/N Ireland/Scandinavea and the old red sandstones of Orkney/NE Scotland [17,19,20] which all naturally carry high levels of Ba [1,2] and low levels of 'free' sulphur. Furthermore, in the case of the Sardinian, Canadian, Scottish MS cluster regions, the local geological veins are sufficiently rich in Barytes ore to support the mining of Ba. Other studies have suggested (without any analytical support) that elevated levels of lead or molybdenum are common to the soil types associated with MS clusters [19,21], but the results of the author's own geochemical analyses have failed to support these hypotheses. Whilst lead levels were moderately raised in two of the locations tested, the widely recognised co-presence of Ba in lead rich strata [1,2] could represent the pertinent factor that has been overlooked.

The low sulphur facet of the abnormal mineral profile within MS ecosystems (see Table 2) is also highly relevant in respect of determining the levels of reactive Ba which can ultimately be absorbed into the biosystem. Low levels of available 'free' sulphur in the soil will considerably exacerbate the problem of Ba/Sr toxicity, since sulphur readily conjugates with Ba and Sr; thereby acting as a 'toxic sink' and preventative against Ba intoxication [22].

The coastal position of many of the MS high risk populations onto the North Atlantic may be associated with their dietary intake of seafoods, such as shellfish and molluscs, which are known to bioconcentrate Ba to excessive levels [1,23]. Seawater of the northern Atlantic is notoriously high in Ba due to the local seabed geology [1], whilst the

additional intensive use of barium drilling muds in the North Sea oil rig drilling industry — particularly around the coast of NE Scotland — has considerably exacerbated the problem of elevated Ba in the marine foodchain since the 1980s [1]. In this respect, the customary consumption of whale meat — as well as shellfish and mussels — amongst the MS risk populations could have unwittingly exposed them to excessive bioconcentrations of Ba due to the whale's dietary intake of algae/plankton which bioconcentrate Ba from the surrounding seawater to excessive levels in their cell membranes [1]. Reference should also be made here to the exclusive reliance of the UK animal feed industry upon the North Sea as its key source of 'fish meal' protein — a common component of concentrated cattle feeds during the 1980s/1990s. Such a practice might have played an aetiological role in the BSE epidemic which emerged in UK bovines, cats and zoo animals during the 1980s/1990s — TSEs representing one of the other classes of neurodegenerative disease that exhibit a tendency to cocluster alongside MS in these Ba-contaminated ecosystems.

The billeting of the military in the MS affected communities [8] of the Faroes, Iceland, Saskatchewan/Alberta borders, Guam, the Gulf war zones, etc, has been associated with the onset of MS and other neurodegenerative epidemics, and this could be correlated to the sudden contamination of the local atmospheres following detonations of Ba based explosives [1,2] during military conflicts or exercises, or due to other military uses of Ba such as radar ducting aerosols [28]. Other routes of Ba exposure in the MS clusters involve the proximity of the individual's home, workplace or water supplies to quarry explosions or the spreading of spent Ba drilling mud across farmland — a waste product of the fast expanding oil and gas well industry that was observed in the Alberta/Saskatchewan MS clusters.

Eco-analyses of MS clusters: materials and methods

The author has conducted a research programme that analysed the levels of 46 elements in the soil/vegetation/water collected from several of the key MS cluster regions around the world.

Soil sample collection/analysis method

Each soil sample comprised a 300 g sample drawn from a mix of 20 columns of dry soil bored with a stainless steel auger; each column having been bored at equidistant spaces along a W shape spanning an area of approximately 5 acres, the area being representative of the region harvested/populated by the MS affected individuals under study. Each column was drawn from the top soil to a depth of 6 in. having taken care to avoid inclusion of root material/surface organic matter and collection of samples near to gateways, roadsides, animal dung, disturbed/excavated or polluted terrain. The 20 columns were collected into a plastic bag, then mixed into an even homogenate, from which a further sample of no more than 300 g was drawn and placed into a small polythene bag, then sealed, labelled and transported to the laboratories at the Department of Geology, Royal Holloway, University of London, Egham Hill, Surrey TW20 0EX, where samples were dried after arriving at the laboratory in forced air flow cabinets. The temperature was maintained below 32 °C during the 12-h drying period and the air was constantly dehumidified. The soil samples were then ground to pass a 2 mm mesh using a hammer mill. The mill was flushed between samples using a small portion of the next sample. Each sample was analysed by standard mass spectrometer analytical procedure.

Vegetation sample collection/analysis method

Each plant tissue sample comprised a 200 g sample representing tissue collected from approximately 10 pickings/diggings taken at equal spacings in a W shape (where possible) across an area of approximately 5 acres that was representative of the region harvested/populated by the MS affected individuals under study. Samples were picked dry and at an appreciable distance from roadsides, gateways, animal manure, mechanically disturbed or 'spot' polluted terrain. The tissue was packed directly into plastic bags, lightly sealed, labelled, refrigerated and then transported to the laboratories of the Department of Environmental Sciences at Derby University, Kedleston Road, Derby DE22 1GB, UK. Each sample was placed in a plastic sieve and thoroughly washed in deionised water. After removal of any roots or soil, the samples were spread evenly on a drying tray and dried in a 90 °C oven to constant weight, and then ground by Christy Norris mill, a small portion of the next sample being used to flush the mill, before collection of the ground material. The samples were then prepared for analysis by dry ashing for non volatile elements and wet digestion in aqua/regia

for volatile elements (e.g. selenium). Analyses was by standard ICP scan.

Results of eco-analyses of MS clusters (see tables)

Working to a mean reference level of Ba in soils at 250 ppm and Ba in pasture vegetation at 10 mg/kg [24,25], levels of barium (and/or strontium) were recorded in the excessive/high ranges in the vegetation (mean: 74 ppm) soils (mean: 1428 ppm) of all MS cluster environments analysed to date, whereas levels remained in the normal ranges (means; 19 and 349 ppm, respectively) within adjoining MS-free control regions (see Tables 1 and 2). Levels of free sulphur were recorded in the low range in the vegetation of the MS cluster regions.

Weymouth, Massachusetts cluster

One high incidence cluster involved 40+ cases of MS that have recently emerged in a middle class population living in a 3 sq. mile block of suburban 'dormitory' housing that is sparsely scattered around the former US military naval airbase at South Weymouth in Massachusetts [26]. A local survey [26] had established that 70% of the MS cases involved people who had been living beneath or near to the incoming/outgoing flight paths of the jet aeroplanes. Samples were drawn close to the homes of the MS victims and the results indicated that Ba, and to a lesser extent Zinc, were the only elements that showed a significant deviation from mean reference levels — Ba was 16-fold elevated in the vegetation and 12-fold elevated in the soils — see Tables 1 and 2. The levels of Ba recorded normal in the identical soil types of the MS-free adjoining area, suggesting that the high Ba recorded beneath the MS affected jet flightpath zone derives from a pollutant source that is linked to the activities of the aircraft — such as a Ba based system of atmospheric cloud seeding for fog dispersion, or from the common practise of adding Ba into jet fuels for capturing sulphur, suppressing exhaust smoke [4], as well as creating a Ba ion atmospheric aerosol [27,28] ducting path — for enhancing/refracting radio and radar signals during military jet practise or battlefield operations.

Aberdeenshire clusters

The three MS cluster foci in Aberdeenshire, NE Scotland identified in the Shepherd thesis [12] during the 1970s are located in the specific areas where paper milling and/or granite quarrying was exclusively prevalent. Furthermore, the drinking water which supplied these MS populations used to be drawn from springs that issue from the Ba rich Dalradian quartzoze mica schist geological series. Another possible source of Ba contamination may have stemmed from the aerial dispersal of Ba based aerosols — such as the barium strontium titanate compounds used for enhancing radar/radio wave transmission [28] — along the flight paths of the military jet 'low flying' test zones that operate over these specific MS affected valleys in Scotland. The author recorded high levels of Ba in all of these Aberdeenshire MS cluster ecosystems, which included levels of Ba at 46 and 694 ppm in the vegetation and soils lying beneath the flight path entering the local military airbase at Lossiemouth.

Table 1 Levels of Ba, Mg, S in pasture vegetation drawn from MS cluster and MS-free adjoining region (Ba in mg/kg dry basis; Mg and S as %)

Cluster	Disease	Ba (range)	Ba source	Mg%	S%	No sample
Weymouth (Ma)	MS, ALS	160 (110–210)	Aeroplane fuel additive	.11	.22	×10
Randolph (Ma)	*MS-free*	*14 (11–17)*	*Soil*	*.16*	*.38*	*×5*
S Guam	MS, PD, AD	53 (30–91)	Volcano/WW2 bombs	.22	NR	×4
N Guam	*MS-free*	*24 (21–27)*	*Soil*	*.41*	*NR*	*×2*
Sardinia	MS, TSE	45 (124–13)	Soil/barytes/explosives	.23	.19	×13
S Sardinia	*MS-free*	*14 (10–23)*	*Soil*	*.46*	*.47*	*×5*
SW Saskatch	MS, TSE	50 (35–64)	Soil/bomb testing	.17	NR	×6
Vermont	*MS-free*	*24 (12–46)*	*Soil*	*.30*	*.47*	*×20*
Fort Collins, Co.	MS, TSE	56 (10–147)	Soil/cement/gypsum	.25	.19	×40
Aberdeenshire	MS	82 (42–121)	Soil/granite/paper mill	.24	.26	×10
Mean MS		74		.20	.21	
Mean MS-free		*19*		*.33*	*.44*	
Mean ref. range [25]		10 (0.5–40)		.37	.35	

Table 2 Levels of Ba/Mg in soils drawn from MS cluster and MS-free adjoining regions (Ba in ppm/MgO as %)

Cluster	Disease	Ba (range)	Ba source	Mg%	No samples
Weymouth (Ma)	*MS, ALS*	*5017 (1745–8290)*	*Aeroplane fuel additive*	*0.49*	*×10*
Randolph (Ma)	MS-free	396 (	Soil	0.53	×5
S Guam	*MS, PD, AD*	*601 (191–1170)*	*Volcano/WW2 bombs*	*1.73*	*×5*
N Guam	MS-free	144 (66–302)	Soil	1.37	×4
Sardinia	*MS, TSE*	*696 (478–1369)*	*Soil/barytes/explosives*	*0.78*	*×14*
S Sardinia	MS-free	367 (290–454)	Soil	1.57	×6
SW Saskatch	*MS/TSE*	*905 (591–2282)*	*Soil/bomb testing*	*0.69*	*×8*
Vermont	MS-free	474 (326–762)	Soil	1.4	×20
Fort Collins, Co.	*MS/TSE*	*568 (345–1091)*	*Soil/cement/gypsum*	*0.69*	*×40*
Aberdeenshire	*MS*	*786 (560–1570)*	*Soil/granite/paper mill*	*0.58*	*×12*
Mean MS		*1428*		*0.82*	
Mean MS-free		345		1.22	
Mean ref. range [25]		250 (100–500)		1.00	

Other co-cluster locations

The author has also observed excess levels of Ba and strontium (Sr) in specific districts within Sardinia, Saskatchewan, Fort Collins (Co), Iceland, NE Scotland and NE Leicestershire (UK) where a high incidence of MS has co-clustered with other types of neurodegenerative disease; particularly the transmissible spongiform encephalopathies (TSEs) and amyotrophic lateral sclerosis (ALS) [29,34] — possibly suggesting that an exclusive type of environmentally induced pathogenesis is shared by all of these neurodegenerative conditions; one that is determined by the prevalence of an abnormal package of eco-factors in these co-cluster environments.

South Pacific clusters

Elevated levels of Sr/Ba were recorded in the miocene volcanic terrain which supports the villages on the southern tip of the isle of Guam [30] — the area representing the 'epicentre' of the well recognised cluster of 'Guam syndrome' involving motor neurone disease, Alzheimer-type dementia (AD), parkinsonism (PD) and MS that simultaneously emerged in those individuals who were commonly exposed to some insidious neurotoxic agent during their early life [31,32]. Whilst the incidence rate of these Guam syndromes used to run at 50× the mean international rate for these conditions, the outbreaks have significantly declined over recent years, suggesting that the causal candidate/s were present during the 1940s–1950s window period [31,32]. Levels of Sr and Ba in the disease-free, non-volcanic north of the island were nearer to normal.

An additional source of artificial Ba contamination was introduced into the specific regions of the South Pacific which subsequently became the neurodegenerative cluster environments. This involved the detonation of Ba based explosives [1,2] during the intensive US bombing raids of world war two, when the coastlines of the Japanese occupied Guam, Rota island, Irian Jaya and southern Japan were specifically targeted by the US aircraft carrier assaults of june/july 1944. This may explain why the high incidence clustering of neurodegeneration simultaneously surfaced in the populations who were occupying all of these specific conflict regions [31,32] — where their syndrome represents a delayed neurotoxic response to the detonation of Ba based explosives. Furthermore, the New Guinea 'Fore' tribesfolk who developed an epidemic of 'Kuru' TSE in the 1950s had accidentally exploded several bombs whilst looting the WW2 bombers which had crash landed in their highland territories during the 1940s [33]. Furthermore, the Fore folk had also scavenged the metal fuselage sheeting (painted with barium based radar absorbing pigments) from the planes and utilised them for tools and cooking pans.

The biochemistry of a Ba initiated MS pathogenesis

Whilst 90% of Ba absorbed into the biosystem is deposited in the bones, the remaining 10% is absorbed into the soft tissues such as the brain and cardiovascular system [1,2]. In this respect, it is not surprising that cases of Ba intoxication frequently simulate inflammatory and neurotoxic

conditions of the nervous system such as Guillain Barre syndrome, fish poisoning (ciguatera) and periodic paralysis [3].

During circumstances of calcium shortage, Ba can replace Ca causing the Ca channels to 'scramble' into a state of rapid fire, inducing an overdrive of the cholinergic and monaminergic neuronal systems [1].

Chronic exposure to the reactive, soluble Ba salts could initiate the pathogenesis of MS [3] via a straightforward pathogenic mechanism based upon the capacity of Ba ions to readily conjugate with sulphates in the biosystem [1–3] – via an electrostatic and non electrostatic interaction with the carboxylate/water molecules (see Fig. 1). The resulting loss of free sulphur deprives the sulphated proteoglycan molecules of their essential sulphur component, whereby the synthesis of a metabolically viable proteoglycan molecule is impaired [35]. Furthermore, Ba can also knock out *S*-proteoglycans when Ba reacts *directly* with *S*-proteoglycans to yield the Ba sulphate; an interaction which is exploited by biochemists for analysing the sulphate content of the proteoglycans [36]

Once the syndecan, perlecan and glypican types of sulfated heparan proteoglycan are deficient within the biosystem, then the proteoglycan-dependent fibroblast growth factor-2 (FGF) signalling system is disrupted, causing a collapse in the proliferation of the oligodendrocyte/astrocyte type 2 progenitor cells that are essential precursors of the mature oligodendrocyte/astrocyte glial cells [37,38]. In this respect, a Ba-induced disruption in the synthesis of these sulphated proteoglycans, blocks the vital participation of these molecules as co-receptors for the growth factors and extracellular matrix molecules which specifically regulate the signal that induces oligodendrocyte/astrocyte progenitor proliferation, migration and adhesion phenomena; which, in turn, blocks the development and structural maintenance of the multilamellar myelin sheaths [37,38] – the central pathogenic mechanism of MS pathogenesis. Furthermore, the Ba-induced disruption in the formation/maintenance of astroglial cells, as well as the oligodendrocytes, could explain why TSEs are co-emerging alongside MS in the animal/human populations who are residing within these high Ba ecosystems; for a disturbance in the metabolism of astroglial cells is a consistent feature of TSE pathogenesis [39].

Ba contamination would also impair the supply of free sulphur required for the disulphide bonding of the peptides that are structurally assembled into the building blocks of the myelin sheath [35]. Furthermore, the loss of the *S*-proteoglycans would disrupt cell cell signalling and the subtle conformational changes surrounding the all important amino acids in the tryptophan peptide of the myelin basic protein that enables serotonin (5HT) to bind [40]. Since 5HT binding to this peptide is regulated by the co binding of both FGF and sulphated proteoglycans to local tyrosine kinase receptors [35,41], it is easy to envision how a Ba-induced impairment of proteoglycan signalling could disrupt the cell to cell signalling that enables 5HT to bind to its peptide domain on myelin basic protein. The resulting cessation of the signal leads to a 'shut down' in the phosphorylation which is normally required to induce the subtle conformational changes within the tryptophan peptide that determines the successful binding of 5HT to myelin

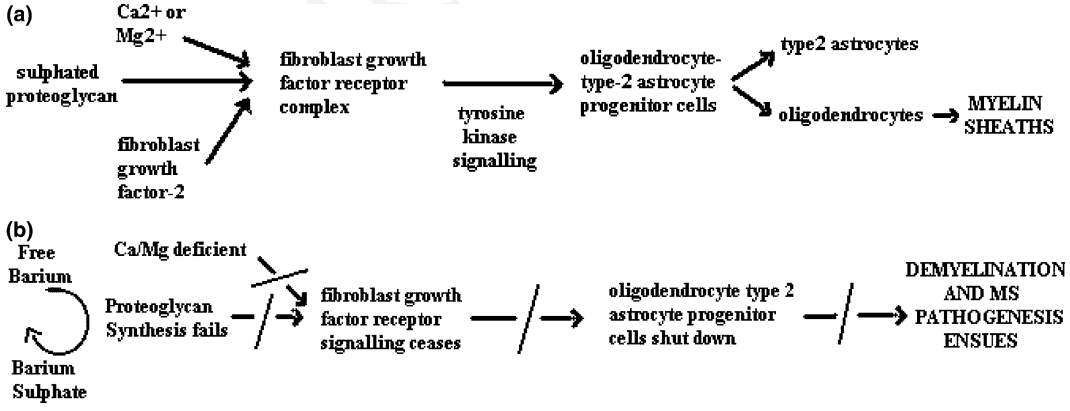

Figure 1 (a) Healthy proteoglycan metabolism. A co-requirement for sulphated proteoglycan, Mg/Ca cations and fibroblast growth factor type 2 in the regulation of the tyrosine kinase receptor complex, which, in turn, regulates the proliferation of the oliodendrocyte progenitors which mediates the synthesis of the myeline sheath. (b) Barium disrupted proteoglycan metabolism and MS pathogenesis. A barium induced sulphur starvation and Mg deficiency disrupts the proteoglycan mediated proliferation of progenitor cells and the production of the myelin sheath.

basic protein [40]. Such an aberration could lead to a successful replacement binding by some opportunist alien 'heavy weight' molecular mimics [41] (e.g. Lysergic acid diethlyamide, Mescaline, amphetamine, cannabis, etc.), where the overall molecular weight of the newly formed 'alien-amino acid' complex is excessive; thereby invoking a lymphocyte mediated auto immune attack on the myelin protein — the key feature of MS/experimental autoimmune encephalomyelitis [40,41,44].

A Ba-induced depletion of endogenous *S*-proteoglycan turnover would also lead to platelet aggregation due to a similar style block in 5HT binding and a disruption of cell cell communication with the platelet adhesion molecule [42,45]. Loss of cell surface proteoglycan binding to superoxide dismutase would result in the proliferation of superoxide generated oxidative stress [45]. There is evidence for both increased platelet aggregation [44] — caused by a block in 5HT uptake [43] — and increased superoxide generated oxidative stress in the pathogenesis of MS [46].

Ba intoxication induces a disturbance of the sodium—potassium (Na—K) ion pump leading to extracellular hypokalemia [1—3], where the Ba ions competitively block passive cellular potassium (K) ion efflux, whereupon continuous activity of the Na—K ion pump leads to an accumulation of K and extracellular hypokalemia — an imbalance in the K channels is evident in the pathogenesis of MS [44].

Discussion and conclusions

The sulphur-capturing facet of Ba intoxication offers a credible explanation for the key demyelinating feature of MS pathogenesis [43]. In this respect, the involvement of other sulphur-capturing organic chemicals and metals, like Mo, Sr, Zn or tributyl tin [3,23], should also be considered as alternative candidates for initiating the breakdown in the proteoglycan-FGF signalling systems that is putatively involved in the pathogenesis of MS.

The key tenet of this hypothesis pivots upon the Ba-induced breakdown in the proteoglycan-FGF signalling systems which normally maintain the oligodendrocyte and type 2 astrocyte progenitor cells [37,38]; thereby ultimately disrupting the synthesis/maintenance of the myelin sheath. This tenet is readily testable in the cell culture model, where oligodendrocyte/astrocyte type 2 progenitor cells are exposed to levels of Ba that reflect concentrations that would be expected to penetrate the brain following chronic atmospheric exposure to Ba in welding fumes or military radar/radio ducting aerosols, or following dietary exposure to Ba contaminants in foods and water. The possibility of a nasal-olfactory route of airborne Ba intake into the brain [47] should also be born in mind when assessing the dose range in the protocol.

Postmortem analyses of MS affected brain in order to establish the distribution and concentration of Ba/Sr/Mo depositions would also be useful.

If the results of any future challenge continue to substantiate the preliminary observations that underpin this hypothesis, then benefits could be gained from developing therapeutic treatments with Ba chelating agents that can cross the blood brain barrier; or, alternatively, by direct treatment with the classes of *S*-proteoglycan that will replenish the biosystem of the specific types of *S*-proteoglycan that have been depleted during the initiating stages of the disease. Pioneering therapy with *S*-proteoglycans is currently being administered to a vCJD in Northern Ireland.

The already established evidence for a disturbed proteoglycan-FGF co-receptor signalling system in the pathogenesis of several types of neurodegenerative disease (AD, PD, MND, TSEs, etc.) [42,48] is advanced by this preliminary report on the novel discovery of elevated levels of sulphur-capturing Ba/Sr elements, combined with low sulphur, in the cluster environments of these neurodegenerative diseases. These observations suggest that chronic or acute-on-chronic Ba/Sr intoxication could play a primary role in the multifactorial aetiology of these diseases.

Furthermore, the analytical observations of the author and others have observed low levels of magnesium (Mg) and Ca in the ecosystems that support these neurodegnerative cluster communities [30,31,49]. This observation of low Ca/Mg provides a further pathogenic explanation for the shut down of the proteoglycan-FGF co-receptors; in that these receptors have a co-dependence upon the presence of Ca and Mg cations if a viable binding of the FGF to its tyrosine kinase receptor is ultimately able to succeed [42]. In this respect an overall multifactorial hypothesis is postulated which decrees that any population that is dependent upon an ecosystem that is characterised by this *aberrant mineral template* — involving high levels of Ba/Sr and low levels of Mg/Ca/S — is compromised into a position of high risk of developing MS, AD or TSE. Whilst many other environmental, stress, idiosyncratic and genetic factors are involved in the aetiological interplay, it is those factors which influence the permeability of the blood brain barrier function — thereby permitting excess uptake of Ba/Sr into the brain — which are of paramount importance in determining our sus-

ceptibility to these diseases. Individual genetics determines which particular class of neurodegenerative wasting disease emerges at the end of the day.

Considering the diverse array of Ba usage within the modern environment [1,2], it is suggested that chronic, or acute-on-chronic exposure to the insoluble salts of Ba could represent a hitherto unrecognised mode of delayed neurotoxicity that is of major public health significance. Further research needs to be channelled into investigating the proposed aetiological association between these reactive alkali earth metals and the origins of MS, as well as the other types of neurodegenerative conditions such as AD, ALS, TSE.

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References

[1] Choudhury H, Cary R. Concise international chemical assessment document: 33-barium and barium compounds. Geneva: WHO; 2001.
[2] Barium, Environmental health criteria 107, International programme on chemical safety. WHO: Geneva; 1990.
[3] Herskovitz S. In: Spencer PS, Schaumburg HH, editors. Experimental and clinical neurotoxicology. 2nd ed. Oxford: Oxford University Press; 2000. p. 225–6. 20–1.
[4] Russell TJ. Additives influencing diesel/kerosene fuel combustion. In: Owen K, editor. Gasoline and diesel fuel additives: critical reports on applied chemistry, vol. 25. Chichester [UK]: Wiley; 1989. p. 65–104.
[5] Lauer K. Risk of multiple sclerosis in relation to industrial activities: an ecological study in four European countries. Neuroepidemiology 1989;8:38–42.
[6] Stein EC, Schiffer RB, Hall WJ, Young N. Multiple sclerosis and the workplace: report of an industry based cluster. Neurology 1987;37:1672–7.
[7] Lauer K, Firnhaber W. Epidemiological investigations into MS in Southern Hesse pt 111. The possible influence of occupation on the risk of disease. Acta Neurol Scand 1985;72:397–402.
[8] Sutherland JM. Multiple sclerosis: fifty years on. Clin Exp Neurol 1983;19:1–12.
[9] Flodin U, Soderfeldt B, Noorlind-Brage H, Fredriksson M, Axelson O. Multiple sclerosis, solvents and pets: a case referent study. Arch Neurol 1988;45:620–3.
[10] Amaducci L, Arfaoli C, Inzitari D. MS amongst shoe and leather workers: an epidemiological survey in Florence. Acta Neurol Scand 1982;65:94–103.
[11] Fischman H. Multiple sclerosis: a new perspective on epidemiological patterns. Neurology 1982;32:864–70.
[12] Shepherd DI. Multiple sclerosis in NE Scotland. MD Thesis, University of Aberdeen, Scotland.
[13] Mauras Y, Allain P, Roques MA, Caron C. Digestive absorption of Ba after oral administration of Ba sulphate for radiology. Therapie 1983;38:109–11.
[14] Clavel JP, Lorillot ML, Buthian D, Gerbet D, Heitz F, Galli A. Intestinal absorption of Ba during radiological studies. Therapie 1987;42:239–43.
[15] Bastarache E. Barium and compounds/toxicology (CASRN 7440-39-3). Integrated risk information system, IRIS toxicological review, US Environmental protection agency.
[16] Baranzini SE, Oksenberg JR, Hauser SL. New insights into the genetics of MS. J Rehabil Res Dev 2002;39(2):201–10.
[17] Rinne UK, Panelius M, Kivalo E, Hokkanen E, Palo J. Distribution of MS in Finland with special reference to some geological factors. Acta Neurol Scand 1966;42:385–99.
[18] Sotgiu S, Pugliatti M, Sanna A, Sotgiu A, Castiglia P, Solinas G, et al. MS complexity in selected populations: the challenge of Sardinia. Eur J Neurol 2002;9(4):329.
[19] Layton W, Aust M, Sutherland JM. Geochemistry and multiple sclerosis: a hypothesis. Med J Aust 1975;1:73–7.
[20] Mykura W. Orkney and Shetland: British regional geology, Institute of Geological Sciences, Natural Environment Research Council. London: HMSO; 1976.
[21] Warren HV. Geology and MS. Nature 1959;15:561.
[22] Pais I, Benton Jones J. The handbook of trace elements. Florida: St. Lucie Press; 1997.
[23] Frausto da Silva JJR, Williams RJP. The biological chemistry of the elements. 2nd ed. Oxford: Oxford University Press; 2001.
[24] Barium: in mineral tolerance of domestic animals (Board on Agriculture). The National Academies Press; 1980. p. 54–9.
[25] Underwood EJ. Trace elements in human and animal nutrition. 4th ed. New York: Academic Press; 1977.
[26] Wilmot D, Tomolillo E. Map of distribution of MS cases at S. Weymouth–Abingdon, Weymouth and Rockland environmental studies (AWARES), Reported in "Clustered cases of MS" Boston Globe, 23rd Febuary 2003.
[27] Paine TO. NASA barium ion cloud. Patent US 3813875, Barium release system to create ion clouds in upper atmosphere. Application No.: US 1972000248761, Patent issue date, June 4th 1974.
[28] Dorsch J. Electronic news, January 11 1999.
[29] Spraker T, Miller M, Williams E, Getzy D, Adrian W, Schoonveld G, et al. Spongiform encephalopathy in free-ranging mule deer, white tailed deer and Rocky mountain elk in northcentral Colorado. J Wildl Dis 1997;33(1):1–6.
[30] Tracey JI, Schlanger SO, Stark JT, Doan DB, May HG. General geology of Guam, Geological survey professional paper 403-A. US Department of the Interior, US government printing office, Washington, DC, 1964, 104pp.
[31] Calne DB, Eisen A, McGeer E, Spencer P. Alzheimer's disease, Parkinson's disease, and motorneurone disease: abiotrophic interaction between ageing and environment? Hypothesis. Lancet 1986:1067–70.
[32] Gadjusek DC. Foci of motor neurone disease in high incidence in isolated populations of East Asia and the western Pacific. In: Rowland LP, editor. Human motor neurone disease. New York: Raven Press; 1982. p. 363–93.
[33] Alpers MP, Kuru. In: Alpers MP, Attenborough RD, editors. Human biology in Papua New Quinea. Melbourne: Clarenden Press; 1992. p. 314 [chapter 16].
[34] Muller WK. Experimental studies on several aspects of MS in Iceland. Bulletin No. 31. Hveragerdi, Iceland: Research Institute Nedri As Publications; 1979.
[35] Devlin TM. Textbook of biochemistry with clinical correlations. 3rd ed. New York: Wiley–Liss; 1992.

[36] Nader HB, Takahashi HK, Guimaraes JA, Dietrich CP, Bianchini P, Ozima B. Heterogeneity of heparin. Int J Biol Macromol 1981;3(6):356–60.
[37] Winkler S, Stahl RC, Carey DJ, Bansal R. Syndecan-3 and perlecan are differentially expressed by progenitors and mature oligodendrocytes and accumulate in the extracellular matrix. J Neurosci Res 2002;69(4):477–87.
[38] Stringer SE, Mayer-Proschel M, Kalyani A, Rao M, Gallagher JT. Heparin is a unique marker of progenitors in the Glial cell lineage. J Biol Chem 1999;274(36):25455–60.
[39] Collinge J, Palmer M, editors. Prion diseases. Oxford: Oxford University Press; 1997.
[40] Root-Bernstein RS, Westall FC. Serotonin binding sites; structure of sites on Myelin Basic Protein, LHRH, MSH, ACTH, Interferon, Serum albumin, ovalbumin and red pigment conc hormone. Brain Res Bull 1984;12:425–36.
[41] Carnegie PR. Interaction of 5-hydroxytryptamine with the encephalitogenic protein of myelin. In: Schmitt FO, Worden FG, editors. The Neurosciences 3rd study program, 81. Cambridge (MA, USA): MIT Press; 1974. p. 925–8.
[42] Kan M, Wang F, Kan M, To B, Gabriel JL, McKeehan WL. Divalent cations and heparin/heparan sulphate cooperate to control assembly and activity of the fibroblast growth factor receptor complex. Am Soc Biochem Mol Biol 1996;271(42):26143–8.
[43] Markianos M, Sfagos C. Altered serotonin uptake kinetics in MS. J Neurol 88 235(4):236–7.
[44] Brain's clinical neurology 6th edition (revised by Sir Roger Bannister). Oxford Medical Publications, Oxford University Press, Oxford, 1986.
[45] Perriman N, Bernfield M. Nature 2000;404:725–8.
[46] Lund-Olesen K. Etiology of MS: role of superoxide dismutase. Med Hypotheses 2000;54(2):321–2.
[47] Hastings L, Evans JE. Olfactory primary neurons as a route of entry for the toxic entry into the CNS. Neurotoxicology 1991;12:707–14.
[48] Perez M, Wandosell F, Colaco C, Avila J. Sulphated glycoaminoglycans prevent neurotoxicity of a human prion protein fragment. Biochem J 1998;335:369–74.
[49] Purdey M. Ecosystems supporting clusters of sporadic TSEs demonstrate excesses of the radical generating divalent cation, manganese, and deficiencies of antioxidant co factors Cu, Se, Fe, Zn Does a foreign cation substitution at Prp's Cu domain initiate TSE? Med Hypotheses 2000;54(2):278–306.