

A case of multiple sclerosis improvement following removal of heavy metal intoxication

Lessons learnt from Matteo's case

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Received: 21 November 2011 / Accepted: 7 March 2012
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Abstract Multiple sclerosis (MS) is a chronic progressive disease of the central nervous system (CNS) provoking disability and neurological symptoms. The exact causes of SM are unknown, even if it is characterized by focal inflammatory lesions in CNS accompanied by autoimmune reaction against myelin. Indeed, many drugs able to modulate the immune response of patients have been used to treat MS. More recently, toxic metals have been proposed as possible causes of neurodegenerative diseases. The objective of this study is to investigate *in vivo* the impact of heavy metal intoxication in MS progression. We studied the case of a patient affected by MS, who has been unsuccessfully treated for some years with current therapies. We examined his levels of toxic heavy metals in the urine, following intravenous “challenge”

with the chelating agent calcium disodium ethylene diamine tetraacetic acid (EDTA). The patient displayed elevated levels of aluminium, lead and mercury in the urine. Indeed, he was subjected to treatment with EDTA twice a month. Under treatment, the patient revealed in time improved symptoms suggestive of MS remission. The clinical data correlated with the reduction of heavy metal levels in the urine to normal range values. Our case report suggests that levels of toxic metals can be tested in patients affected by neurodegenerative diseases as MS.

Keywords Chelation therapy · Multiple sclerosis · Toxic heavy metals · EDTA

Introduction

Multiple sclerosis (MS) is an acquired, inflammatory, demyelinating, neurodegenerative disease of the central nervous system (CNS). The onset of disease occurs in adults at young age (between 20 and 40 years) and less frequently in children and adolescents (Reiber et al. 2009; Ibrahim and Gold 2005). Neurological impairments (attacks) can be followed by asymptomatic periods, e.g., the pathology can present a relapsing-remitting course. Progression of the disease is generally accompanied by presence in the CNS of focal inflammatory lesions which are evidenced using magnetic resonance imaging (MRI). Among the mechanisms involved in the pathogenesis of MS an autoimmune

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reaction against a myelin-related antigen has been identified, although the aetiology is unknown. Current therapies to treat MS include immunosuppressant agents (as mitoxantrone and azathioprine), broad-spectrum immunomodulatory agents (as glatiramer acetate and interferon β) and monoclonal antibodies (as rituximab and natalizumab) (Milo and Panitch 2011). More recently oral fingolimod, a non-selective sphingosine 1-phosphate receptor agonist, which is endowed with immunomodulating activity on leukocyte trafficking through secondary lymphoid organs, has been approved to treat MS (Bolli et al. 2011; Cohen et al. 2010). Many studies have proposed the association of neurodegenerative diseases with toxic metal (especially aluminium, lead and mercury) exposition and accumulation in the CNS (Kumar and Gill 2009; Zahran et al. 2009; Taber and Hurley 2008). In particular, cadmium and mercury have been shown able to disrupt mitochondria of neuronal cells by increasing intracellular reactive oxygen species (ROS) which directly inhibit neuronal Janus kinase (Jak) tyrosine kinase activity (Monroe and Halvorsen 2009). Both ROS-induced enhanced lipid peroxidation and advanced glycation end products have been suggested as activators of signalling pathways, causing formation of pro-inflammatory cytokines. Inflammation is a process actively related to the onset of several neurodegenerative diseases, since an extra-cellular insult to neurons could trigger the production of inflammatory cytokines (IL-1 β , TNF α and IL-6) by astrocytes and microglia (Rojo et al. 2008). We have hypothesized that toxic metals could play a role in favouring the induction of insults to neurons sufficient to promote neuro-inflammation. A method useful to remove toxic metals is represented by the chelation therapy, because the chelating agents are able to bind these metals and create complexes which are excreted in the urine. The above reported therapies for MS have provoked many side effects and in particular the progressive multifocal encephalopathy (PML) was associated with natalizumab (Linda et al. 2009). Here we describe the case of a patient affected by metal intoxication who developed remission of MS following chelation therapy.

Materials and methods

We studied clinical symptoms, analysed blood, cerebrospinal fluid, and performed genetic analysis and

MRI of a patient for about 15 years. The patient has been subjected to the “chelation test” with the aim to evidence possible heavy metal intoxication. Indeed, he was invited to collect the urine samples before and after the intravenous treatment with the chelating agent EDTA (ethylene diamine tetraacetic acid, e.g., calcium disodium edetate, 2 g/10 ml diluted in 500 ml physiological saline, Salf, Brescia, Italy) administered in about 90 min. The time of urine collection following chelation lasted 24 h. Urine samples stored in sterile vials were sent to the Laboratory of Toxicology (Doctor’s Data Inc., St. Charles, IL, USA). Urine heavy metal concentrations were determined by Inductively Coupled Plasma-Mass Spectrometry (atomic absorption spectrometry, which guaranteed precision and accuracy of measurements) and were expressed in micrograms per g ($\mu\text{g/g}$) creatinine.

Written informed consent was obtained from the patient for publishing this case report and relevant images.

Results

A previously healthy 19-year-old man displayed sub-acute vision loss, diplopia, pain with eye movements as the first symptom of optic neuritis in April 1997. Analysis of serum and cerebrospinal fluid by isoelectric focusing, performed in August 1997, evidenced oligoclonal bands which predicted MS following optic neuritis. MRI (using gadolinium as contrast) was also performed and displayed focal hyper-intense surfaces (data not shown). In July 1998 disturbance of fine motor skills in the right hand appeared; it was followed by paresthesia at level of the body right side, and gait ataxia, which were cured with intravenous steroid administration. In September 1998 diagnosis of MS according to the original Mc Donald criteria was made (Barkhof et al. 1997; Polman et al. 2005). Suppressive therapy with azathioprine (50 mg twice a day taken orally) was begun in July 1999 and stopped in November 2001. In 2003 the patient was subjected in Germany to the removal of four dental amalgams. After a brief period of well-being, a slow relapse occurred (possibly following the exposure to paint and formaldehyde vapours used in his house). In November 2005 the patient developed leg spasticity, diplopia, gait ataxia, absence of left hand control, bladder dysfunction, significant tiredness. Blood tests revealed high bilirubin

levels (1.33 mg/dl), high TSH levels (2.970 μ U/ml), low levels of vitamin D3 (25-OH) (7.8 ng/ml) and alteration in the ratio of reduced/oxidized glutathione. The latter related to the genetic variant resulting in lack of expression of the gene for one of the two most relevant human isoenzymes of cytosolic glutathione S transferase (GST), e.g., the mu1 (GSTM1) enzyme, which (together with GST theta1 or GSTT1) is involved in detoxification of hydrophobic electrophiles or oxidized lipids derived from the metabolism of xenobiotics (Bolt and Thier 2006). In April 2006 the patient returned to Germany and underwent the ozone autohemotherapy associated with endovenous infusion of vitamin B, vitamin C, alpha lipoic acid and glutathione. Following these treatments, he had a remission of previous symptoms. However, such remission lasted about 2 months and, when the patient returned to Italy, in spite of the therapy with ozone and the intramuscular administration with vitamin B12, the symptoms worsened and inability to walk appeared. In August 2006 the patient was hospitalized in Bologna and treated with methylprednisolone pulse therapy (1,000 mg/day for 5 days). Successively, he was hospitalized in Milan, where the diagnosis of progressive secondary MS was made. At admission patient blood and urinary tests were normal, except for higher levels of total bilirubin (1.83 mg/dl), direct bilirubin (0.33 mg/dl) and indirect bilirubin (1.46 mg/dl). A cranial MRI scan performed in 11 August 2006 with gadolinium as contrast showed two “activated” lesions located at right periventricular temporal region and at left semioval center (Fig. 1). Such MRI has been defined worse in comparison with the previously performed. The neurologist treated the patient with two cycles of methylprednisolone pulse therapy ($5 \times 1,000$ mg) and one endovenous treatment with mitoxantrone. Moreover, the patient underwent physiotherapy, without evidence of improvement in MS symptoms.

In September 2006, the possible heavy metal intoxication of the patient was examined.

The levels of toxic metals measured before “challenge” with EDTA did not differ from those of controls (normal reference range of toxic metals, as reported by the Laboratory of Toxicology).

The levels of heavy metals obtained after “challenge” with EDTA were: aluminium 325 μ g/g creatinine (maximal value ≤ 25), lead 64 μ g/g creatinine (maximal value ≤ 2), mercury 25 μ g/g creatinine (maximal value ≤ 3). The patient was subjected to

EDTA chelation therapy (disodium edetate administration twice a month) and declined the treatment with mitoxantrone after the second intravenous injection of this drug. The MS symptoms progressively disappeared and in February 2007 he used a bicycle for some kilometres. The patient took glutathione daily (ultrathione 1,000, once a day) and the antioxidant deutosulfazyme (Cellfood, Eurodream, La Spezia, Italy) (eight drops three times a day). The patient continued the EDTA chelation therapy and in July 2007 the urine levels of heavy metals after EDTA “challenge” were: aluminium 81 μ g/g creatinine, lead 23 μ g/g creatinine, mercury 18 μ g/g creatinine. The following EDTA administrations were efficient in further removing lead and mercury; in fact the urine levels of these metals were reduced in 26 May 2008 to 3 and 2 μ g/g creatinine, respectively, whereas aluminium levels displayed some variations in the time. In May 2008, after 32 chelation therapies, the patient was subjected to a new MRI with gadolinium as contrast. Following MRI, which displayed new demyelinating areas, the patient’s symptoms worsened (reduced sensibility at left foot level, worsened balance and dizziness). In 26 June 2008 for the first time urine levels of gadolinium after EDTA challenge were measured: noteworthy, high levels (61.6 μ g/g creatinine; normal range ≤ 0.4), due to previously performed RMI, were shown. Concomitantly, the urine levels of aluminium, measured after EDTA challenge, were increased to 197 μ g/g creatinine and those of lead to 6.2 μ g/g creatinine. The following chelation therapies were able firstly to remove gadolinium, whereas aluminium levels further increased, as revealed by the values obtained in 15 July 2008 and 10 October 2008 (387 and 334 μ g/g creatinine, respectively). Successively, EDTA treatments were effective in reducing urine gadolinium levels to 7.7 μ g/g creatinine, and aluminium levels to 212 μ g/g creatinine in January 2009.

In 2009 the patient symptoms improved definitively: he was subjected in total to 60 chelation therapies. The modifications of urine toxic metal levels from July 2007 until today are reported in the Fig. 2. Now the therapy is administered once a month.

Discussion

The case history of the patient described here shows that recovery from MS occurred following the

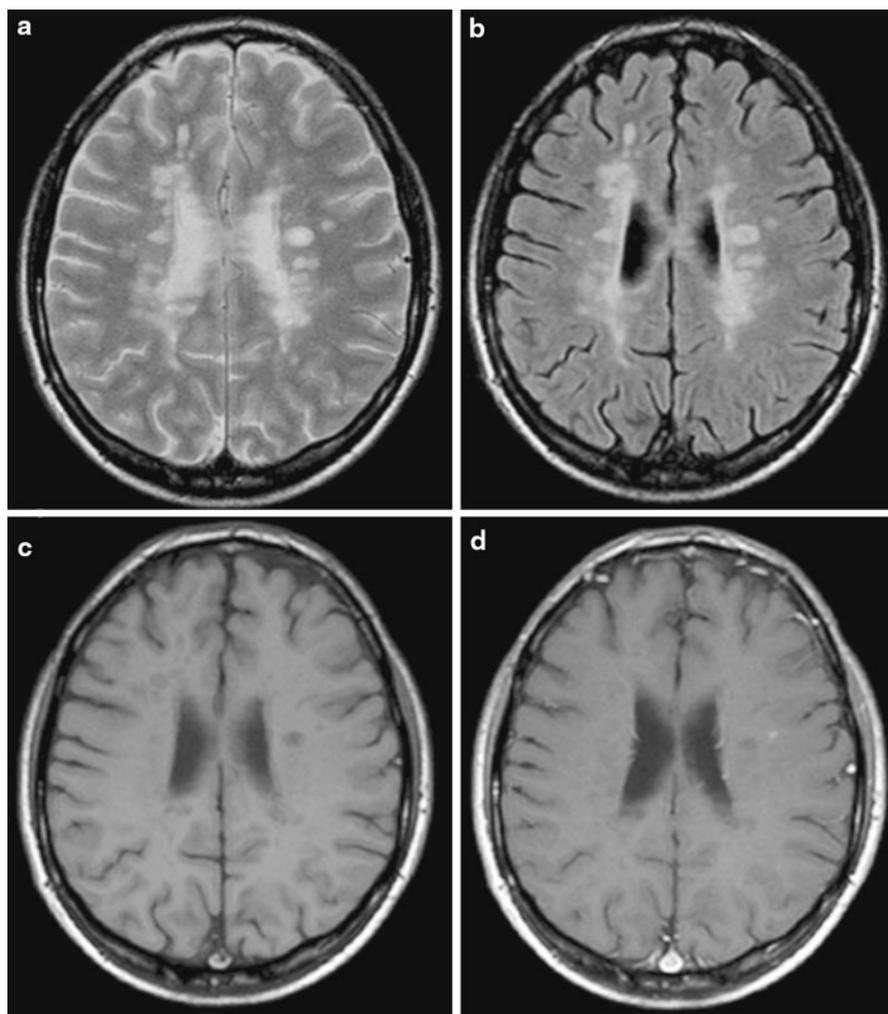


Fig. 1 MRI of patient's brain performed in August 2006. **a** T2-weighted imaging showing grey and white matters and focal lesions; **b** FLAIR axial cut showing hyperintense signals (lesions); **c** T1-weighted image showing locations of a-specific

lesions; **d** T1-weighted post-contrast (gadolinium) image showing two “activated” lesions located at right periventricular temporal region and at left semioval center

removal of patient's toxic metals by means of chelation therapy. The first sign of MS developed by patient was optic neuritis, as displayed by many patients affected by MS: in fact injury to the optic nerve, brainstem and cerebellum is able to lead to characteristic syndromes affecting both the afferent and the efferent visual pathways (Graves and Balcer 2010). Moreover, cerebrospinal fluid analyzed by electrophoresis has shown a split to form so called oligoclonal bands, which consist of proteins from activated lymphocytes and plasma cell clones (Skov et al. 2010). MRI for the diagnosis and monitoring of

patient by means of gadolinium-enhanced imaging has been used (Bakshi et al. 2004). The patient presented null expression of the GSTM1 gene, which codifies the enzyme belonging to a super-family of glutathione S-transferases that metabolizes a broad range of reactive oxygen species and xenobiotics. The absence or decrease of such gene has been recently related to important diseases. In particular, GSTM1 has been associated to regulation of vascular smooth muscle cell proliferation, migration and oxidative stress. Genetic variants causing a decrease in expression of GSTM1 may permit an environment of exaggerated

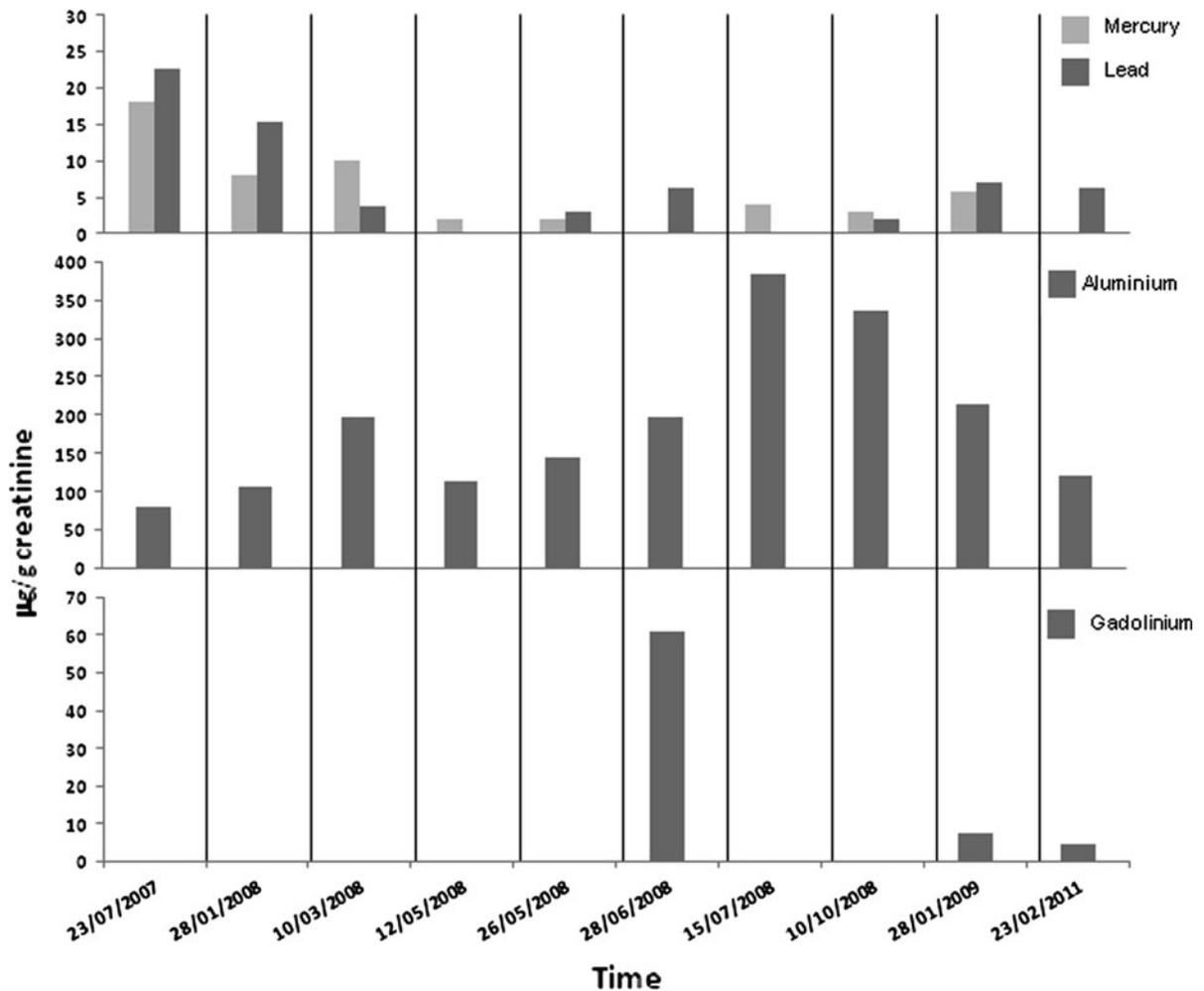


Fig. 2 Modifications of heavy metal levels, evaluated in urine after “challenge” with EDTA, at different times from 2007 to 2011

oxidative stress, leading to susceptibility to vascular remodelling and atherosclerosis (Yang et al. 2009). Moreover, the epistatic effect of GSTM1 and GSTT1 deletion polymorphism has interestingly shown a risk factor for increased susceptibility to mercury exposure, suggesting that the above enzymes have implications for the metal detoxification capability of the human organism (Gundacker et al. 2007). Finally, more recently, GSTM1 and GSTT1 null genotypes have been identified as potential biomarkers of predisposition for developing leukopenia (Goncalves et al. 2010). The patient revealed elevated levels of some heavy metals (aluminium, lead and mercury) in urine samples collected following chelation treatment. We measured heavy metal content in the urine samples

because blood levels reflect only recent exposure, as demonstrated for lead exposure (Rosin 2009). Heavy metals leave blood and enter into brain and other organs few days after intoxication. Indeed, it is difficult to show increase in the metal content in blood, following an old exposition. Previously, elevated urinary excretion of aluminium and iron in patients affected by MS has been demonstrated, whilst increased levels of biomarkers of oxidative damage (malondialdehyde and 2-thiobarbituric acid-reactive substances) were not found (Exley et al. 2006). The increase of aluminium excretion appeared similar to that associated with aluminium-chelation therapy with desferrioxamine (Ott et al. 1986). We did not observe in our patient spontaneous urinary excretion of toxic

metals before chelation treatment. However, the binding of chelating agent EDTA to toxic metals enabled the patient to progressively eliminate elevated urinary concentrations of aluminium, lead and mercury. EDTA performs stable complexes with metals in function of mass, pH and affinity (Corsello et al. 2009). The tissue of origin of toxic metals before removal by EDTA is possibly the CNS, but also other tissues are involved. However, it is difficult to establish the tissue of origin of such metals in our patient.

Accumulation of toxic metals in human organs may induce deleterious effects. For instance, low-level environmental lead exposure was able to accelerate progressive renal insufficiency in patients without diabetes who had chronic renal disease. In these patients, repeated chelation therapy with calcium disodium EDTA has improved renal function (evaluated as significant increase in the glomerular filtration rate) and slowed the progression of renal insufficiency (Lin et al. 2003). Just some years ago the CNS was described as the principal target for a number of metals: in fact inorganic compounds of aluminium, arsenic, lead, lithium, manganese, mercury and thallium were investigated for their neurological and behavioural effects in humans (Clarkson 1987). In particular, lead has been demonstrated able to disrupt heme synthesis (the loss of heme-containing enzymes should affect mitochondrial functions impairing energy metabolism) and to interfere with neurotransmitters. Methyl-mercury has been shown able to damage the protein synthesis machinery producing focal damage to specific susceptible areas in the adult brain, whereas depolymerization of reassembled microtubules in developing CNS was also shown (Taber and Hurley 2008). Aluminium was primarily implicated in senile dementia in dialysis patients (Clarkson 1987). More recently, it has been demonstrated that neurotoxicity exerted by aluminium, lead and mercury may be due to the interference of these metals with inositol 1,4,5-triphosphate-mediated calcium release and also with the microsomal Ca^{++} sequestration mechanism, so altering microsomal Ca^{++} flux (Pentyala et al. 2010). Moreover, other evidences have been proposed to explicate heavy metal neurotoxicity. Indeed, the neurotoxic response to methyl-mercury has been shown to be dependent on the cell type, neural stem cells being more susceptible; moreover, methyl-mercury has been shown able to

trigger multiple cell death pathways that may be concomitantly activated (Ceccatelli et al. 2010). Brief exposure to lead during neurogenesis was demonstrated efficient in directly affecting cell survival and process development, potentially altering cortical arrangement (Davidovics and DiCicco-Bloom 2005). Aluminium-induced neural cell death (displayed as apoptosis) has been recently related to inactivation of the Bax gene, which is involved in the maintenance and survival of neurons and neuron-supporting cells, as glial cells (Zhang et al. 2010). Interestingly, a synergistic neurotoxicity of a metal mixture (arsenic, cadmium and lead) in the developing brain has also been shown (Rai et al. 2010).

Our patient had beneficial effects after removal of his dental amalgams in 2003. Mercury from silver dental fillings has been previously shown as an etiological factor in MS (Siblerud and Kienholz 1994). However, the transient benefits achieved were cancelled following the exposition to possible new sources of heavy toxic metals (described as contact with painting during house working).

In the patient's history, the performance of a new control MRI in 2008 favoured the worsening of his MS symptoms. This result was possibly attributable to neurotoxicity induced by gadolinium used as contrast. Gadolinium, a rare-earth lanthanide metal, has been shown efficient in provoking impaired mitochondrial function and oxidative stress (Feng et al. 2010) and able to trigger endoplasmic reticulum stress-related signal transduction in rat cortical neurons (Xia et al. 2011). Due to some important limitations of MRI findings in MS, such as the poor correlation with clinical disability, we suggest that use of gadolinium can be limited to first diagnostic neuro-imaging (Sicotte 2011). Following the use of gadolinium, elevated levels of this metal in the urine samples of the patient were assessed. Noteworthy, the successive use of chelation therapy was able to firstly reduce urine gadolinium content instead of aluminium (which appeared increased from June 2008 until January 2009), in function of elevated amounts of the former metal. In fact, the ability of EDTA to bind toxic metals seems to be related not only to affinity but also to amount of metals. When gadolinium returned to control values, EDTA treatment progressively reduced also urine aluminium content.

Some considerations about drugs used in MS therapy are warranted. Natalizumab, a humanized

monoclonal antibody that binds to the $\alpha 4$ integrin adhesion molecule at the $\beta 1$ and $\beta 7$ epitopes, is an integrin inhibitor which prevents extravasation of T and B cells into the brain and consequently reduces inflammatory/immune reactions in lesions of MS. PML, a rare demyelinating disease induced by polioma JC virus, appeared in 2004 as a complication of natalizumab treatment. The possible mechanism of natalizumab-induced PML is related to the ability of the drug to force stem cells and pre-B cells to migrate from the bone marrow, since they cannot bind to vascular endothelial cell adhesion molecules due to inhibition of own $\alpha 4$ integrin expression. JC virus, which resides in a latent state in the bone marrow, can migrate to the peripheral circulation, using B cell and its DNA-binding proteins to initiate viral multiplication (Major 2009). Subclinical reactivation of JC virus occurring in natalizumab-treated patients is possibly due to a transient drop in the JC virus-specific cellular immune response (Chen et al. 2009). Mitoxantrone, an anthraquinone-type anti-cancer agent used clinically in the therapy of human malignancies, has been used for treatment of refractory MS, but it presents many side effects as risk of cardiotoxicity and leukaemia (Wundes et al. 2010). Other drugs, as interferon β -1b, are poorly tolerated by patients and can frequently induce lymphopenia and depression (Plosker 2011).

In the specific case here described, the patient's detoxification from heavy metals seems to create the environmental conditions useful to improve the clinical signs of MS. We previously used the chelation therapy to cure a patient who was treated many years ago with mercury-containing pharmaceuticals and developed neurologic symptoms (Corsello et al. 2009). It has been recently demonstrated that EDTA chelation therapy, without added vitamin C, decreased oxidative DNA damage and lipid peroxidation (Roussel et al. 2009). Indeed, chelation therapy displays also antioxidant properties which can further support heavy metal detoxification, especially in patients impaired to proceed with their elimination (e.g., bearing genetic defects of GST enzymes). Even if our results show an important link between heavy metal intoxication and MS progression, more evidences have to be reported to confirm such suggestion.

Acknowledgments We thank MD, who encourage us to publish his clinical case, with the aim to possibly help other patients.

Conflict of interests The authors declare that they have no conflict of interests.

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