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Clinical note

Altered homeostasis of trace elements in the blood of SCA2 patients

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ABSTRACT

Spinocerebellar ataxia type 2 (SCA2) is a neurological disorder characterized by cerebellar dysfunction. The possible association between metals and neurodegenerative diseases is under constant investigation, with particular focus on their involvement in oxidative stress and their potential role as biomarkers of these pathologies.

Whole blood samples of SCA2 patients and of healthy individuals were subjected to multi-elemental analysis by inductively coupled plasma-mass spectrometry (ICP-MS). Reduced levels of manganese and copper were found in SCA2 patients, while zinc and vanadium concentrations were significantly higher in patients compared to controls. Copper, manganese and zinc are cofactors of many enzymes (such as superoxide dismutase, SOD) involved in the cellular antioxidant response, whereas vanadium is a transition metal able to produce reactive radicals.

A marked decrease of the antioxidant response has been previously reported in SCA2 patients. We suggest that an unbalance of transitional elements in the blood may reflect altered antioxidant homeostasis in SCA2 patients and could constitute a future peripheral biomarker for this disease. In addition, we suggest a possible role of vanadium in the altered lipid metabolism of SCA2 patients.

1. Introduction

Autosomal dominant spinocerebellar ataxias (SCAs) are genetically heterogeneous neurological diseases characterized by Purkinje cell degeneration causing cerebellar dysfunction. Spinocerebellar ataxia type 2 (SCA2) is the second most prevalent spinocerebellar ataxia subtype worldwide after spinocerebellar ataxia type 3 [1]. The highest world prevalence rate of SCA2 was registered in Holguin province in Cuba [2].

In Italy, the proportion of SCA patients with SCA2 is 47% (the Ataxia Center, Chicago University). This rare neurodegenerative disease is characterized by uncoordinated movements, decreased muscle tone, tremors, poor tendon reflexes, nystagmus, polyneuropathy, dysphagia, chorea, Parkinsonism and dementia [3]. The severity and the age of onset of SCA2 vary, in the majority of cases it becomes symptomatic from the third to the fourth decades of life; however, SCA2 is more rapidly progressive when onset happens in the second decade of life [4].

SCA2 is caused by the expansion of a CAG triplet repeat located in the 5′coding region of the ataxin-2 gene; the mutant protein then contains a segment of polyglutamines [5]. The pathogenic effects of SCAs involve accumulation of a mutated/misfolded cytoplasmatic protein – Ataxin 2, which is located in several tissues and neurons. Ataxin 2 interacts with poly(A)binding protein 1 and assembles into polyribosomes, which probably have a function in RNA metabolism and in regulating cellular mRNA turnover [6]. Intracellular protein aggregates and widespread neuronal loss in the cerebellum have been observed in the brains of SCA2 patients [7].

In recent years, oxidative stress has been shown to be related to several neurodegenerative disorders such as Friedreich ataxia (FA), Huntington disease (HD) [8], and Ataxia-Telangiectasia (A-T) disease [9]. Oxidative stress is the end point of chronic neurodegenerative disease, but is also related to Autism Spectrum Disorder and other neuropsychiatric disorders [10]. The cellular antioxidant system, designed to control the flux of reactive oxygen species (ROS), consists of several antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT). An excess of ROS generation results in a wide range of neural disorders and also aging; toxicity of free radicals causes damage to proteins and DNA and leads to cellular apoptosis [11].

SCA2 has been previously related to oxidative stress, particularly to

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altered activity of key antioxidant enzymes [4,12,13]. In particular, Cornelius et al. investigated the level of mitochondrial oxidative stress by assessing superoxide levels in fibroblasts from SCA2 patients and controls, and found that SCA2 cells displayed a significantly increased amount of oxidative stress compared to control cells.

Altered homeostasis of trace elements has been linked to the etiology of many neurodegenerative syndromes [14]. In particular, Bocca and coauthors [15] found a lower manganese concentration in the blood of Amyotrophic Lateral Sclerosis (ALS) patients compared to healthy individuals; while Roos and coauthors [16] reported an increased level of copper in the blood of ALS patients. Several investigations have reported higher levels of copper in the blood of Alzheimer's disease (AD) patients and high manganese levels in the blood of Parkinson's disease (PD) subjects relative to controls [17].

Some essential elements are, in fact, essential cofactors for antioxidant enzymes such as cytoplasmic Zn/Cu-SOD (SOD1) and mitochondrial Mn-SOD (SOD2), which act as bulk scavengers of superoxide radicals [18,19].

In a previous investigation, we discovered altered metal concentrations in the blood of Ataxia Telangiectasia (A-T) patients, another neurodegenerative disease in which ataxia is one of the main symptoms. In particular, we found that copper levels were significantly higher in A-T patients and zinc levels were significantly lower [9]. Moreover, a reduction of Cu/Zn-SOD and Mn-SOD activities were also observed in A-T lymphoblastoid cell lines (LCLs), suggesting that altered homeostasis of zinc and copper may play a role in the pathology of A-T. In this study, we measured the levels of 15 metals (arsenic, beryllium, cadmium, cobalt chromium, copper, iron, manganese, nickel, lead, antimony, selenium, thallium, vanadium and zinc) in the blood of SCA2 patients, with the aim of assessing metal concentrations in the patients' blood compared to controls, and investigating whether transitional metals involved in the oxidative stress response could constitute a possible peripheral biomarker of this disease.

2. Patients and methods

2.1. Subjects

We enrolled 20 SCA2 adult patients (10 males and 10 females) diagnosed with SCA2, which was confirmed by genetic testing, and 18 healthy adult individuals as controls (10 males and 8 females). Subjects were age-matched, with a mean age of 49 years in patients and 47 years in healthy individuals.

The study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) 1964, and was approved by the committee of the Medical Sciences Dept. (DSM-ChBU). Patients (or their legal representative) provided their informed consent.

Venous blood was collected, as previously described [9]; briefly, 1 mL of blood was added to HNO_3, microwave digested (ETHOS 1 system, Milestone S.r.l, Italy), and processed together with a certified reference material (Seronorm trace elements whole blood level 2). Metal concentration analyses were performed with A Thermo X series II ICP-MS instrument, as previously described [9], utilizing a Collision Cell Technique (CCT), to remove interferences.

2.2. Statistical analysis

The D'Agostino-Pearson normality test was utilized to determine the distribution of values, which were normally distributed. The Student's *t*-test was utilized for comparing between the control group and the patient group. Results were considered statistically significant using p values of < 0.05. Graph Pad Statistics Software Version 6.0 (GraphPad Software, Inc., USA) was utilized for statistical calculations.

Table 1
Metal concentrations ($\mu g\,L^{-1}$ ± S.D) in the blood of SCA2 patients and controls.

Metals	*Patients (N = 20)*	*Controls (N = 18)*	*Statistics (Unpaired t-test)*
As	3.4 (± 2.9)	2.0 (± 2.2)	n.s.
Be[1]			
Cd	0.80 (± 0.53)	0.71 (± 0.40)	n.s.
Co	0.57 (± 0.35)	0.56 (± 0.19)	n.s.
Cr	22 (± 1.5)	19 (± 1.2)	n.s.
Cu	**866 (± 45)**	**1116 (± 68)**	**p = 0.0001**
Fe	523648 (± 5041)	495857 (± 4523)	n.s.
Mn	**16 (± 3.1)**	**21 (± 4.2)**	**p = 0.001**
Ni[1]			
Pb	62 (± 8.5)	70 (± 12)	n.s.
Sb	4.2 (± 1.7)	3.4 (± 1.2)	n.s.
Se	119 (± 19)	125 (± 35)	n.s.
Tl[1]			
V	**6.5 (± 1.0)**	**3.7 (± 0.8)**	**p = 0.03**
Zn	**5860 (± 900)**	**5189 (± 999)**	**p = 0.04**

Note: statistically significant results are indicated in bold.
[1] Concentrations of these elements were below the limit of quantitation of the method.

3. Results

Whole blood concentrations of the analyzed metals in SCA2 patients and healthy individuals are shown in Table 1, and were expressed as μg/L ± standard deviation (S.D).

Of all the essential trace elements, copper and manganese levels were significantly lower in the blood of SCA2 patients ($p = .0001$ and 0.001, respectively) while zinc levels were significantly higher ($p = .04$) (Table 1, Fig. 1).

Levels of the other essential elements, i.e. cobalt, chromium, iron and selenium did not significantly differ between patients and controls.

Arsenic, antimony, cadmium, lead, thallium and vanadium are metals with no recognized biological functions, and are thus considered non-essential for life. Among them, only vanadium levels (Fig. 1) were found significantly higher in SCA2 patients ($p = .03$).

4. Discussion

Many previous investigations have linked the origin of neurodegenerative disorders (such as AD, PD, HD, ALS, Friedreich's Ataxia and AT) to increased oxidative stress in neuronal cells, thus suggesting the involvement of microelements such as Zn, Cu and Fe [9,14–17].

Essential trace elements play a crucial role in the correct functioning of the human nervous system. Neuronal cells do not function properly when there is a copper imbalance, and Cu dyshomeostasis has been linked to AD and ALS [20]. Moreover, in Mendelian disorders such as Wilson and Menkes diseases, the progressive neurological dysfunction is due to a disturbance of Cu metabolism, with an accumulation of copper in the brain and other organs [20].

Zinc is the second most abundant microelement in nervous tissue, after iron. Decreased Zn concentrations have been implicated in the pathophysiology of PD, AD, Friedreich's Ataxia [21] and, recently, AT disease [9].

Superoxide dismutases are antioxidant enzymes that are able to catalyze the conversion of superoxide anions to hydrogen peroxide, providing the cells with a defense mechanism against ROS [22]. Cu and Zn are co-factors of the main SOD isoform, SOD1, which exerts most of the total cellular SOD activity in the cytosol. An equilibrated molar ratio between Cu and Zn is necessary for the correct functioning of this antioxidant enzyme. When we studied A-T patients [9], we argued that the lower zinc levels, together with the higher copper levels found in patients, could be the cause of the functional reduction of SOD1 observed in A-T cells.

Conversely, in the blood of SCA2 patients, we observed a higher zinc

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