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CASE REPORT

Iron and Parkinson's disease

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Abstract

In this case presentation, a man with a diagnosis of Parkinson's disease was treated with Chelation Therapy against iron without iron serum level correlation. The patient, who suffered from motor and non-motor symptoms of the disease, showed an improved condition after the Therapy. This clinical test was evaluated with UPDRS III score. The rationale and the limits of the Therapy are discussed. This case suggests that iron-dependent oxidative stress could represent a promising therapy for this dramatic disease; the necessity to deeply study the iron metabolism in neuro-degeneration appears really significant.

Abbreviations"

6OHDP	- 6-hydroxy-dopamine
AD	- Alzheimer's disease
DAT	- dopamine transporter
DFO	- deferoxammine
DMT1	- divalent cation transporter 1
HC	- Huntington's corea
IRE	- iron regulatory elements
IRP2	- iron regulatory protein 2
MTPT	- 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
NADH	- nicotinamide adenine dinucleotide
NADPH	- nicotinamide adenine dinucleotide phosphate
NET	- norepinephrine transporter
PD	- Parkinson's disease
ROS	- reactive oxygen species
Tfr1	- transferrin receptor 1
TH	- tyrosine hydroxylases
SERT	- serotonin transporter
SNPC	- substantia nigra pars compacta
UPDRS	- unified Parkinson's disease rating scale

CLINICAL CASE

In November 2003, LL was a 61 years-old-man weighing 75 kg. His father had died for heart failure and his mother probably suffered from diabetes. In September 2003, this man, who had cutaneous lesions of psoriasis for 20 years, initially suffered from depression and apathy. After serological exams, he was visited by a Neurologist from the "Miulli Hospital" of Acquaviva delle Fonti (Bari) who formulated the diagnosis of "extra-pyramidal syndrome " and suggested the use of *L-dopa/carbidopa* 100mg /25 mg four times a day. After two months the clinical conditions were not good and the therapy was integrated with *selegiline* 5 mg, one tablet os a day and *amantadine* 100 mg tablet, one tablet three times a day.

After one year, in November 2004, because of the development of tremors *cabergoline* was added to the therapy (5 mg tablet, one tablet os a day).

In the next five years, the therapy was modified with the introduction of *bromocriptine* 2,5 mg tablet three times a day, *melevodopa/carbidopa* 100/25 mg, one tablet os in the "off-period", *delorazepam* 1 mg tablet, one mg os at 11.00 pm as a result of the development of sleep disorders.

In November 2010, he presented with depression, critical bradycinesia and the therapy was modified: levodopa/carbidopa 100/25 mg tablet, one tablet four times a day; *levodopa/carbidopa* 250/25 tablet, one tablet os a day; *ropirinole* 2 mg tablet, one tablet three times a day; *sertraline* 50 mg one tablet a day, selegiline 10 mg, one tablet a day.

In March 2011, following the observation of orthostatic hypotension, *midodrine* was added to the therapy, 10 drops os three times a day, and because of the severity of symptoms including long periods in a day of apathy, acynesia and crying fits, the therapy was modified with *rotigotine* 8 mg, one *trandermic plaster* a day, *levodopa/carbidopa/entacapone* 200/50/200 one tablet three times a day; *levodopa/carbidopa* 250/25 + *levodopa/carbidopa* 200/50 mg rm for a total of 1,050 mg day of *levodopa*, *clonazepam gtt*, 10 drops os for the sleep and *mirtazapine* 30 mg cpr, one tablet a day for his depression and sleep disorders.

In November 2012, due to the seriousness of the situation and the decline of general conditions with an UPDRS III score of 87, we decided to investigate serological heavy metals levels but we didn't observe any important alteration. However, we decided to introduce Chelation Therapy with *deferoxiammine* and *ascorbic acid* because we have observed that heavy metals serological levels are not always correlated with clinical conditions and, due to the dramatic clinical situation and the literature background in which iron is considered important for the development of PD, we added *deferoxammine* 500 mg im and *ascorbic acid* 200 mg im one time a day to therapy for three months.

After three months of therapy we observed an improvement of the clinical condition. The patient was able to walk, freezing, bradycinesy, depression, agitation were reduced and we decreased the therapy to deferoxammine 500 mg and ascorbic acid 200 once a day for two times a week.

After six mounts the UPDRS III score was substantially stable and on June 2014 the value was 28 (Figure 1).

The Hoen e Yahr score was 4 at the beginning of the therapy; after one year the value was 3 (Figure 2).

RESULTS

Therapy and clinical course

The therapy had the ability to reduce motor symptoms and abolish some non-motor symptoms. In particular hallucinations, delusions, depression, anxiety, apathy were reduced; dopamine dysregulation syndrome's symptoms were completely abolished. Daytime sleepiness and leg pain had completely disappeared. Constipation and fatigue were improved. The freezing was reduced and the necessity of help to do the activity of daily living were particularly decreased. No side effects were found and serological values of iron, ferritin, hemocromocitometric test were found in the normal range

Deferoxammine is a chelating agent against iron and aluminium (Brown *et al.* 1982; Nebeker *et al.* 1984). This drug was the first aluminium chelating agent to be introduced in clinical practice and it was administered with good efficacy either intramuscularly or intraperitonally (Ciancioni i*et al.* 1984; Molitoris *et al.* 1987).

Savory *et al.* have demonstrated that DFO can reverse the tau aggregates following two days of treatment in aluminium-induced neuro-fibrillary degeneration in rabbits. The associations with ascorbic acid is intended to guarantee the reduction of Fe^{3+} to Fe^{2+} and to improve the binding of this metal ion to DFO (Herbert 1999). This activity could be useful to move iron ions and reactive oxygen species iron-dependent from trigger sites like mitochondria and cellular nucleus to areas in which the metal could explain specific physiological functions (myelinogenesis in particular).

DISCUSSION

PD is the second most common neuro-degenerative disease after AD. It affects about 1% of the population older than 60 years. The characteristic feature is the loss of dopaminergic neurons in the substantia nigra pars

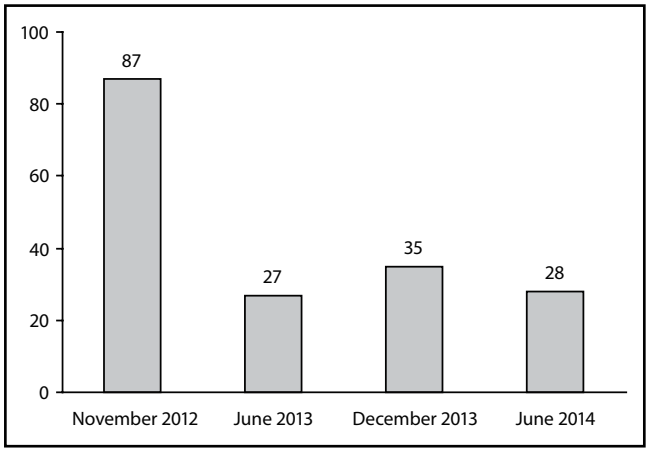

Fig. 1. UPDRS III score during the therapy.

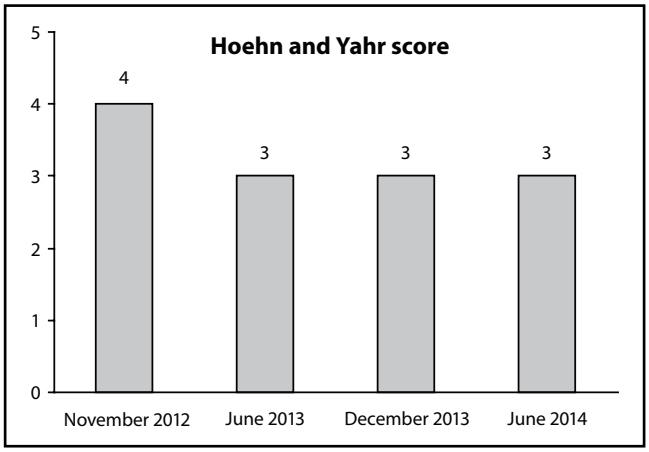

Fig. 2. Hoehn and Yahr score during the therapy.

compacta (SNPC), located in midbrain (Schapira *et al.* 2004).

The role of iron in this disease has been hypothesized after some observations.

First, the intra-neuronal concentration of iron correlates with the UPDRS motor score (Zhang *et al.* 2010): in PD patients there is a specific increase of this metal in the substantia nigra and the lateral globus pallidus, by approximately two fold in comparison with age-matched controls (Gotz *et al.* 2004; Zecca *et al.* 2004). In patients with hemocromatosis, an iron storage disease, it is necessary to obtain symptoms for an increase of iron of 10–20 fold (Mohamed *et al.* 2004).

Secondly, the intracellular aggregates called Lewy Bodies, a hallmark of PD, are composed by alpha synuclein, other proteins like IRP2, an important iron metabolism sensor, and the same iron (Takanashi *et al.* 2001). The aggregation of these proteinaceous bodies is promoted by this metal (Golts *et al.* 2002) and, at the same time, the administration of DFO blocks alfasynuclein aggregation (Munch *et al.* 2000).

Third, the uptake and the neuro-metabolism of iron is critical to understand the relationship between this metal and neurodegenerative disorders.

There are two theories about iron uptake in the brain. For the first one this crucial role is mediated by transferrin and its receptor Tfr-1, with an endocytosis mediated mechanism. Other studies suggest an important role for DMT1: this carrier is expressed in rat substatia nigra both with and without the iron regulatory element (IRE) in neurons, astrocytes and microglia, but not in oligodendrocytes (Song *et al.* 2007). DMT1 could be related with parkin if we consider that an over-expression of parkin causes a down-regulation of DMT1 expression, and in particular of its 1B isoform (Roth *et. al*. 2010). The relation with DMT1 is suggested by the fact that the mutation in DMT1 in rats causes less sensibility to neurotoxins MPTP and 6OHDP which are responsible of Parkinsonism (Salazar *et al.* 2008).

Also, the export and the accumulation of iron from and within the cells are related to PD. The iron export system is represented into neurons, astrocytes, microglia and oligodendrocytes of the susbtantia nigra thanks to the expression of ferroportin and hephaestin (Salazar *et al.* 2008).

6OHDP induces the downregulation of these export proteins, with the consequent accumulation of the metal in the neurons. The reaction to this oxidative stress is represented by the over-expression of the human ferritin heavy chain (H-Ferritin) with the modulation of iron homeostasis and the restoration of the activity of ubiquitin-proteaosome's system (Zhu *et al.* 2010).

At the same time, L-ferritin is localized in neuromelanin granules (Kaur *et al.* 2009).

If ferritin can represent a physiological iron chelator and the chemical iron chelating agents exert neuro-protective effects against the MTPT and 6 OHDP (Youdim *et al.* 2007), neuro-melanin can block Fenton's reaction, inhibit the oxidation of ascorbic acid and, with the formation of iron-neuromelanin complex can block the formation of the neurotoxic dopamine quinones (Zecca *et al.* 2008). In this way, neuro-melanin exerts a chelating agent role. Ex adiuvantibus, we observe that drugs commonly used in the therapy, like lisuride, protects against iron-induced lesions (Double *et al.* 2003) probably dopamine agonist can reduce the dopamine synthesis: in fact, in this way, there is a decrease of iron into neuro-vesicles (Ortega *et al.* 2007).

If iron is neuro-toxic, it is clear that this is important especially for neurons involved in dopamine metabolism. This metal is an important cofactor of tyrosine hydroxylases (TH) and MAO, two enzymes involved in dopamine biosynthesis and metabolism respectively.

For iron neurotoxicity the presence of DAT is important. In this way, the complex iron-dopamine can enter in neurons, but also with NET or SERT (Paris *et al.* 2005). Arreguin *et al.* (2009) demonstrated that iron forms a complex with dopamine and that Fe-dopamine which protected isolated hepatocytes against hypoxia-re-oxygenation-induced injury (Siraki *et al.* 2000) because in these cells DAT isn't present (Lienert and Kozlowski 2012).

The precursor of dopamine, L-dopa, also forms a complex with iron^{3+} (Mohamed *et al.* 2004) and this supports the idea that these complexes could be formed especially into dopaminergic neurons.

Once inside the neuron, Fe-dopamine complex undergoes some reactions to produce the radical leukoaminochrome-o-semiquinone which is extremely reactive with oxygen (Segura-Aguilar *et al.* 1998) and then neurotoxic (Arriagada *et al.* 2000). Thus, there are the formation of superoxide radical, its dismutation to H2O2 and the depletion of NADH/NADPH. In this way, there is an affection against the mitochondrial electron transport chain: the consequently cellular energy collapse, and so, cell death is mediated by ATP depletion. Iron and dopamine, in this way, cause apotosis (Wang *et al.* 2008). It's a vicious circle: upon oxidation of Fe-dopamine complex, Fe^{3+} is reduced to Fe^{2+}, with consequently, the formation of hydroxyl radical from H_2O_2 generated in the dismutation of superoxide radical. The Fenton Reaction oxidizes Fe^{2+} to Fe^{3+} so new complexes between Fe and dopamine can be formed (Lienert and Kozlowski 2012).

While Fe-dopamine complex exerts a neuro-toxic activity, and to do this it require the presence of DAT and the inhibition of DT-diaphorase, norepinephrine-Fe^{3+} complexes aren't neuro-toxic. This fact represents an important evaluation for the practical use of some drugs.

The metal based ROS production in specific regions of the brain based on iron levels can generate the peroxidation of polyunsaturated fatty acids in membrane phospholipids, with the consequent production of reactive aldehydes. In this way, it causes damage to proteins with carbonyl functions. The damaged proteins are

overwhelming the ubiquitin-proteasome system with the generation of Lewy's Bodies and others intracellular inclusions, hallmark of PD and many neuro-degenerative disorders, like AD and HC (Lienert & Kozlowski 2012).

CONCLUSIONS

Although a multifactorial pathology like PD cannot be addressed by focusing on a single feature, the role of iron, not necessarily correlated with a serum marker, can represent a promising therapeutic goal. Probably the use of new oral chelating agents could be much more comfortable. The idea that iron dependent oxidative stress can represent an important, but not the only one, feature of different kinds of disease requires future insights.

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