Ceruloplasmin gene variations in patients with different neurological diseases

Sara Scannapieco[1], Maurizio Morelli[1], Grazia Iannello[3], Monica Gagliardi[2], Dania Salvino[1], Alessandra Fratto[1], Fabiana Novellino[2], Giuseppe Nicoletti[2], Grazia Annesi[2], Aldo Quattrone[3]

[1]Institute of Neurology, Department of Medical and Surgical Sciences, University Magna Graecia, Catanzaro, Italy.
[2]Institute of Molecular Bioimaging and Physiology, National Research Council, Section of Germaneto, Catanzaro, Italy.
[3]Institute of Neurology, Department of Medical and Surgical Sciences, University Magna Graecia, Catanzaro, Italy; Institute of Molecular Bioimaging and Physiology, National Research Council, Section of Germaneto, Catanzaro, Italy.

Objective

Ceruloplasmin (Cp), a multi-copper enzyme, plays an important role in maintaining iron homeostasis in the central nervous system preventing free radical injury. Cp oxidizes ferrous iron into ferric form and thus keeps the intracellular level of dangerous ferrous iron to a minimum. Furthermore, iron deposition in the brain can also promote conformational change in alfa-synuclein. A possible involvement of Cp in the pathogenesis of Parkinson's disease (PD) has been supported both by immunohistochemical studies that revealed a co-localization of Cp and Lewy bodies, than by genetic studies, that dimostred Cp gene variations in PD patients. These variations had never been investigated in the other patients, even if low level of serum Cp was found in patients with various diagnoses, expecially with movement disorders. Our objective was to perform a genetic testing in all patients with hypoceruloplasminhaemia.

Materials and Methods

We assesed the level of serum Cp in patients suffering different neurological diseases, admitted to our neurological clinic from Jenuary 2010 to December 2014. Patients with normal (≥20 mg/dl) serum Cp value were removed. An informed consent to undergo genetic analysis was obtained from 79 out of 126 patients and six known variations of the Cp gene (I63T, P477L, T551I, R793H, T841R, D544E) were analysed. Particularly, up to now genetic analysis was performed on 18 patients. In 10 patients we found the wild type gene: 1 of them were suffering from PD, 4 of them were affected from unclassifiable parkinsonism, 3 were suffering essential tremor, 1 had cerebellar ataxia and 1 had frontotemporal dementia. In 3 patients we found a T551I variation: 2 of them had a diagnosis of unclassifiable parkinsonism and the other one a focal epilepsy diagnosis. In 3 patients we found D544E variation: 1 was affected from spastic paraparesis and other 2 from essential tremor. In 1 patient we found a R793H variation and he suffering from dementia. In 1 patient we found P477L variation and he was affected from multiple system atrophy.

	Wild type gene	Variation T551I	Variation D544E	Variation R793H	Variation P477L
Unclassifiable Parkinsonism	••••	••			
Essential Tremor	•••		••		
Parkinson's disease	•				
Frontotemporal Dementia	•				
Dementia				•	
Focal Epilepsy		•			
Multiple system atrophy					•
Cerebellar ataxia	•				
Spastic Paraparesis			•		

Discussions and Conclusions

Iron plays an essential role in many biological processes. Mutations and polymorphisms in genes encoding for proteins involved in iron metabolism have been linked to the pathogenesis of PD. Our results show that patients with low levels of Cp not necessarily have variations in the Cp gene. Furthermore, patients with the variations of the Cp gene are not homogeneous according to the clinical phenotype. Further studies on larger sample of subject are needed to understand which role the Cp plays in several neurological diseases, as well as in PD.

References

1. Ling H, Bhidayasiri R Reduced Serum Caeruloplasmin Levels in Non-Wilsonian Movement Disorders. European Neurology. 2011;66:123-127.
2. Hochstrasser H, Bauer P, Walter U, Behnke S, Spiegel J, Csoti I, Zeiler B, Bornemann A, Pahnke J, Becker G, Riess O, Berg D. Ceruloplasmin gene variations and substantia nigra hyperechogenicity in Parkinson disease. Neurology. 2004;63:1912-7.
3. Zhao N, Xiao J, Zheng Z, Fei G, Zhang F, Jin L, Zhong C. Single-nucleotide polymorphisms and haplotypes of non-coding area in the CP gene are correlated with Parkinson's disease. Neurosci Bull. 2015;31:245-56.

SIN SOCIETÀ ITALIANA DI NEUROLOGIA

XLVI CONGRESSO NAZIONALE
10-13 OTTOBRE 2015 – GENOVA