Amyotrophic Lateral Sclerosis and Multiple Rare Tumors in homozygous SOD1 Asp90Ala mutation: Just a Chance Association?

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Background

❖A subset of Familial and Sporadic Amyotrophic Lateral Sclerosis (ALS) is characterized by mutations of the Cu,Zn Superoxide Dismutase 1(SOD1). This enzyme is localized in cytosol, mitochondria and nucleus and its dysfunction can have a role in almost all of pathogenetic pathways suggested in ALS (oxidative stress, protein misfolding, cytoskeleton alterations)[1]. More than 100 different SOD1 mutations have been reported to date, all of which show autosomal dominant transmission, except for the D90A and the D96N mutations which may show also recessive inheritance[2].

❖When inherited with a recessive transmission, D90A-SOD1 mutation is associated with an **homogeneous phenotype** characterized by **lower limbs onset, slow progression and sensory involvement**. In the latter phases of the disease, in this subset of patients, a **cerebellar involvement** was also described, even if in a low percentage [3].

❖ While SOD2 has a well documented role in oncogenesis (related to its scavenger function of keeping low levels of ROS), new scientific evidences show that **SOD1 is overexpressed in cancers** and its activity, although not completely cleared, seems to be of critical importance to the survival of tumor cells, **expanding the role of SOD1 to cancer** [4]**.**

Case Report

❖A 46 years old caucasian man comes to our attention for walking difficulties due to **lower limbs weakness** and **disbalance.** Symptoms begun *3 years earlier*, with a slowly progressive course and a story of **occasional stumbling when walking**.

❖Anamnestic story revealed that, at the age of 45, after the occasional finding of inguinal lymphadenopathy he underwent lymph node biopsy that turned out to be a **secondary localization of Kaposi's sarcoma**, subsequently treated with surgery obtaining remission of the disease.

❖**Family history was unremarkable.**

❖*Neurological examination at admission* showed fasciculations in four limbs, brisk deep tendon reflexes and paraparesis. *Electromyography* revealed **denervation activity, altered MUPs** (increased duration and width), **fibrillations and fasciculations** suggestive of motor neuron disease; no alterations in sensory and motor conduction; *Brain and Spinal Cord MRI* were normal and *muscle biopsy* showed neurogenic atrophy.

❖**Genetic analysis** of **SOD1** gene was performed and a **homozygous D90A substitution in exon 4 was found**. Accordingly, **ALS was diagnosed and Riluzole treatment was started**.

Figure 1

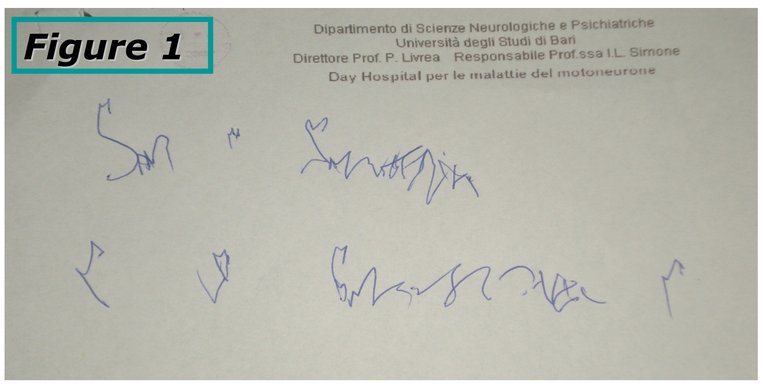
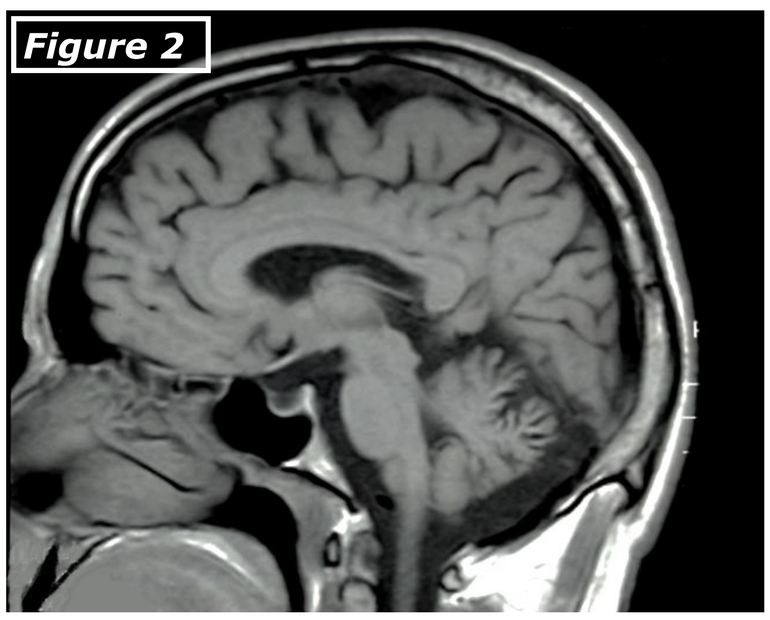


Figure 2



❖In the following 8 years, the patient showed progressive deterioration of motor performance with **weakness and atrophy in the four limbs** and, later, **dysarthria, dyspnea and occasional dysphagia.**

❖At the age of 55 the patient developed significant **cerebellar signs with limb ataxia, intentional tremor of head and writing incoordination(figure 1).** A **new brain MRI revealed cerebellar atrophy (figure 2)** whereas previously MRI scans were described as normal; serum Anti-Hu/Anti-Yo antibodies assay and genetic analysis for SCA mutations resulted negative.

❖In February 2015 – *at the age of 60* – after presenting sporadic nipple serous secretions, he underwent FNAB of a **breast lump that revealed to be a estrogen-dependent (ER and PR +) papillary infiltrating carcinoma** subsequently treated a radical mastectomy according Madden technique. Computed Tomography Staging and subsequent follow-up examinations showed no repetitive lesions in other organs. The patient is now taking hormone therapy with tamoxifen.

Discussion and conclusions

Our case confirms that patients with homozygous D90A-SOD1 mutation constitute a **phenotypically characteristic subset of ALS**, with **cerebellar signs during** paretic phase, underlining that ALS is a **multisystem disorder,** not confined to the voluntary motor system [3]**.**

This case also suggests that **homozygous D90A mutation could deeply alter SOD1 scavenger function** and **ROS homeostasis.** This altered "ROS balance" could possibly lead to **complex cellular damages resulting in a number of possible events including both neurodegenerative processes and carcinogenesis [5]**. Gain and loss of function murine or cellular models are ongoing to confirm or refute this hypothesis.

References:

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2)Battistini S et al, J Neurol 2005;252:782-788.

3)Mezei M et al, J Neurol Sci 1999; 169: 49–55

4)Papa L, et al. Genes & Cancer Jan 2014; 5: 15-21

5)Sabharwal SS. Et al. Nat Rev Cancer Nov 2014; 14(11):709-21