Multiple Sclerosis and Neurofibromatosis type1: case report

A. AMIDEI, L. PASQUALI, L. PETRUCCI, I. CALABRESE, A. IUDICE, U. BONUCCELLI

Department of Clinical and Experimental Medicine, University of Pisa/Department of Neuroscience, Neurology Unit, AOU-Pisa

INTRODUCTION:

Neurofibromatosis type 1 (NF1) or Von Reckligausen disease is characterized by multiple café au-lait spots and skin neurofibromas, and is caused by abnormal activity of the tumor suppressor gene NF1; about 50% of patient present a new mutation of NF1 gene without affected relatives. The association of neurofibromatosis with multiple sclerosis (MS) has been rarely described, more frequently in patients with primary progressive MS.

CASE REPORT:

We describe a 36 year old woman diagnosed with Neurofibromatosis type 1 in childhood. She showed congenital cafè-au-lait spots, Lisch nodules of the iris, axillary freckles and cutaneous neurofibromas.

At the age of 27, as part of investigations related to the underlying disease, she performed a brain MRI, which showed a focal demyelination but no other investigation were performed at that time.

At the age of 34 she developed paresthesias to the right emisoma and right-hand dystonia. The brain and cervical spine MRI showed demyelinating areas both in the brain and in the spinal cord without gadolinium enhancement (Fig.1). Two oligoclonal bands were found in the CSF.

There was no history or signs for any reumatologic disease such as Behcet's disease (no genital or oral ulcers), Sjogren's syndrome (no dry eye or mouth), Sarcoidosis (chest x ray and calcium level were normal), SLE (no sunlight sensitivity or butterfly rush), Lyme disease (no tick bite). Furthermore she did not present enlarged lymph nodes, joint inflammation, Raynaud's phenomenon. Blood autoantibodies (ANA, ANCA, rheumatoid factor, anticardiolipin, lupus anticoagulant) were negative such as marker of infectious disease like Brucellosis, syphilis, HTLV-1 infection and herpes zoster. VEPs showed prolonged P100 latency bilaterally, indicating subclinical optic nerve lesions. The patient recovered with intravenous steroid administration and at the age of 35 she started treatment with glatiramer acetate. Since then she had no relapses or new lesions at MRI scan.

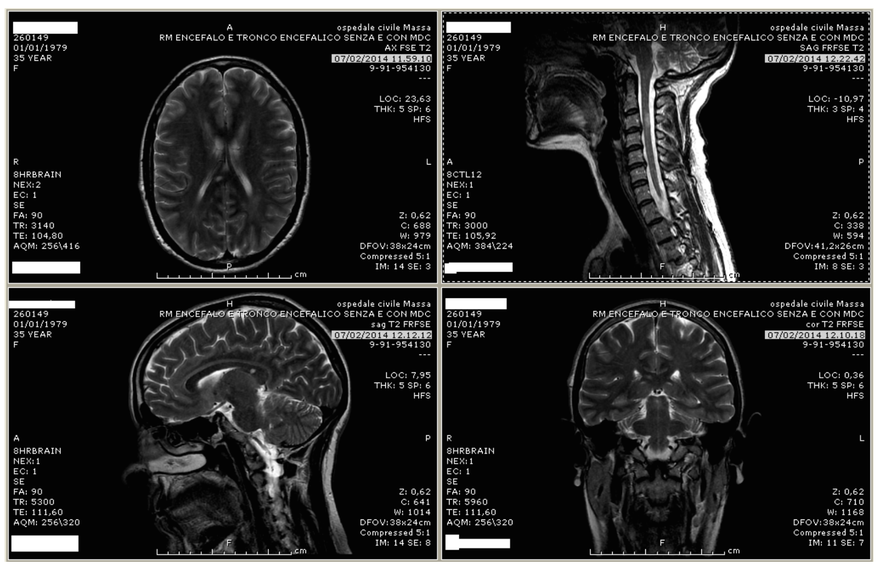

Fig1: MRI T2 image showed increased signal intensity near the corpus callosum and in the c-spine.

DISCUSSION:

In the present case, NF1 was diagnosed according to National Institutes of Health Consensus Development Conference diagnostic criteria for NF1 (Tab 1). The patient also fulfilled McDonald criteria revision 2010 for the diagnosis of relapsing-remitting MS.

Table 1 Diagnostic criteria for neurofibromatosis 1 (NF1)

(NIH consensus development conference 1988)[3]

- 6 or more café au lait macules (>0.5 cm in children or >1.5 cm in adults)
- 2 or more cutaneous/subcutaneous neurofibromas or one plexiform neurofibroma
- Axillary or groin freckling
- Optic pathway glioma
- 2 or more Lisch nodules (iris hamartomas seen on slit lamp examination)
- Bony dysplasia (sphenoid wing dysplasia, bowing of long bone ± pseudarthrosis)
- First degree relative with NF1

Tab 1: Diagnostic criteria for NF1

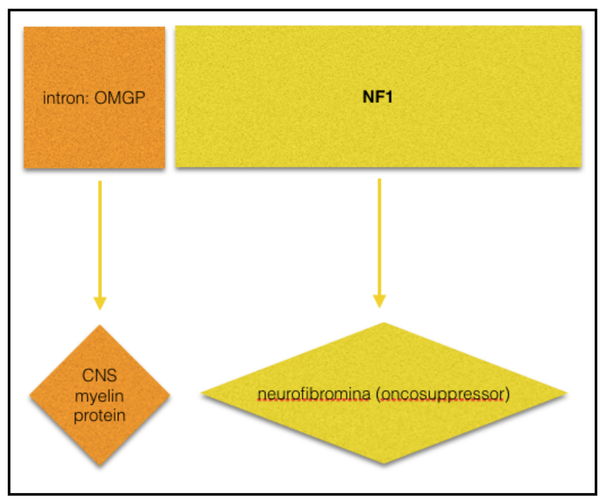

Fig 2: NF1 gene and his products

The association of MS with NF1 is very rare and only 13 case reports have been documented in the literature right now. About 8/11 cases (two cases described not in english were excluded), 72%, had MS in the form of primary progressive subtype and this form is not a common subtype of MS occurring only 10-15% in MS populations. Only one case was in the form of relapsing-remitting. Six of nine patients (66%) had de novo mutation of NF1 gene. Usually new mutations occur in about half of NF1 populations (Tab 2)

AGE AT ONSET	MS TYPE	MRI findings	OCB	TREATMENT	RESPONSE
Female 42 yrs	PP	Multiple area of increased SI in T2 in white matter of both cerebral hemisphere	+	Intravenous methyl prednisolone	IMPROVED
Female 23 yrs	PP	NOT DONE (CT showed several areas of low density in a periventricular areas)	+	UK	UK
Female 26 yrs	PP	Multiple area of increased SI in T2 at periventricular and both cerebral hemispheres	+	Intravenous methyl prednisolone	IMPROVED
Female 42 yrs	PP	Multiple area of high signal lesions In T2 at white matter of both cerebral hemispheres, pons and cerebellar hemispheres	UK	UK	UK
Male 44 yrs	PP	Multiple high signal lesions in lower part of the medulla down to upper cervical cord	UK	Intravenous methyl prednisolone	NOT IMPROVED
Male 19 yrs	RR	Multiple areas of altered signal in the white matter + Some enhanced lesions	+	Intravenous methyl prednisolone	IMPROVED
Female 30 yrs	SP	Multiple areas of altered signal in the white matter of both cerebral hemispheres (corpus callosum, centrum semiovale, periventricular regions)	+	Intravenous methyl prednisolone	IMPROVED
Male 46 yrs	PP	Multiple lesions in both cerebral hemisphere, predominantly at periventricular white matter	+	Intravenous methyl prednisolone	MILD TRANSIENT BENEFIT
Female 28 yrs	SP	Multiple periventricular white matter lesions	+	dexamethasone	IMPROVED
Male 24 yrs	PP	Multiple area of increased SI in T2 at periventricular white matter, corpus callosum bilaterally and right side of midbrain	-	Intravenous methyl prednisolone	NOT IMPROVED
OUR CASE Female 27 yrs	RR	Areas of altered signal in the white matter of corpus callosum and in the C-spine	mild+	Intravenous methyl prednisolone	IMPROVED

Tab 2: Cases documented in the literature.

Genetic association between NF1 and MS has been hypothesized, focusing on two distinct entities : the OMGP-gene (oligodendrocyte-myelin glycoprotein gene), an intron of NF1 gene, whose product is a CNS myelin protein and on NF1, which codes for neurofibromin, a protein that regulates cellular proliferation and differentiation. In NF1 patient, the OMgp gene may not function normally and promote demyelination in susceptible MS patients. However, this hypothesis has not been well accepted due to the fact that OMgp altered gene is present only in about 50% of the population NF1-SM. Moreover, mutation in OMgp gene is also detected in a normal population and MS population in the same percentage. Furthermore NFG1 mutation may also affect the immune system, leading to uncontrolled cellular proliferation of Schwann cells, this determining an immune over-response to oligodendrocytes antigens expressed in the central nervous system (Fig. 2)

NF and MS association is still debated since a causal relationship between the two diseases is not yet clearly defined.

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