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Editorial

The Origin of Facial Palsy in Multiple Sclerosis

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Multiple Sclerosis (MS) is an autoimmune neurodegenerative disease that affects several people especially in North America and Canada. In 2013, 33 individuals over 100,000 were affected from MS; the estimated increase for 5 years of observation ranged from an average of 4.7 per 100,000 in high-income countries to just 0.04 per 100,000 in the low-income countries.[1]

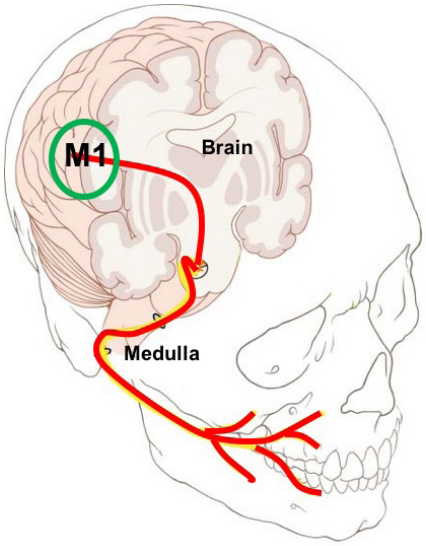
Women are more affected than men (2.3-3.5:1), but in men, the disease is usually more aggressive and has a worse prognosis than in women.[2]

MS is a demyelinating disorder in which the immune system attacks the neural structures in the central nervous system (CNS)[3]; this mechanism is determined by a particular class of cells-*Microglia*- thathave been identified as responsible of the degenerative process. These cells, that belong to the macrophage family, have the ability to move and they can easily migrate in different part of CNS[4] and due to their two different phenotypes, an aggressive one, called M1, that induce neurodegeneration and, a protective phenotype (M2) that has neuroprotective ability[3] they may be induce demyelination and regeneration in different phases of MS, as for example, in the relapsing and remitting disease.

In the active (relapsing) stage of MS, microglia M1 induces demyelination in the area of CNS where they currently are located. If the area interested is a motor one, the patient manifests movement disorders as stiffness or motor fatigue, in case of an attack in a sensory area the sensorial perception will be the affected one.

The facial pathway, that starts in the periphery with the terminal branch of the facial nerve and ends up to the M1 area of cortex (Figure 1), may be attacked by microglia and a demyelinating process that involves one or more areas of this pathway may be symptomatic as facial palsy (FP).

Figure 1. *The Image Summarizes the Facial Pathway from Periphery (Terminal Branch of Facial Nerve) to the Brain Motor Cortex Area (M1)*



Authors report that around 7% of patients affected by MS experienced one episode of FP at least once in their life, but some controversies are still open about the origin of this symptom.

How many of these FPs are central and how many may arise from a peripheral involvement of facial nerve?

We reviewed the literature from 1997 to 2014 and we identified from a total of 16 articles, that most of the MS patients suffered from central facial involvement when they presented with a FP (Table 1).

Three authors, unfortunately, did not report details about the site of the lesions so we were not able to completely under-

Table 1. *Summary of Papers that Cite Facial Palsy in Patients with MS*

Authors	Year	Study type	Sex	Facial	MRI results
Saleh[7]	2016	Case Report	Man	yes Right side	Three lesions in the supratentorial, periventricular region. Two on the right side, one on the left (sizes between 8-13 mm). In spine small lesion at the level of the right caudal pons, inferior to the facial nucleus
Jens[8]	2015	Case Report	Woman	yes Right side started with numbness	Lesion in the floor of 4th ventricle at the pons and two in the right cerebral white matter and cerebellum
Sarigul[9]	2014	Case Report	Woman	yes Left side	Lesions in right parietal and left fronto-parietal areas
Lassemi[10]	2014	Cross-Sectional	73% women, 27% men (400 patients)	17% of sample	Not available
Danesh-Sani[11]	2013	Prospective	32% men, 68 % women (500 patients)	yes 19% of subjects	Lesion in the brain
Lee[12]	2013	Case Report	Man	yes Right side	Lesion in the midline of dorsal pons
Renard[13]	2012	Case Report	Woman	yes Left side	Lesions in the left pontine tegmentu
Uzawa[14]	2011	Case Report	Woman	yes Left side	Lesion in the left facial colliculus
Ivankovic[15]	2011	Case Report	Woman	yes Right side	Lesions in the supra and infratentorial region of the brain (periventricular, corpus callosum, pons, cerebellum
Lin[16]	2010	Case Report	Man	yes Left side	Lesion in the lateral walls of the lateral ventricles
Soltanzadeh[17]	2008	Prospective	41 Women, 12 men	yes	Not available
Kwon[18]	2008	Case Report	Woman	yes Right side started with numbness	Lesion in the right cerebellopontine angle involving the Roof Entry Zone (REZ)
Zadro[19]	2008	Retrospective	18 not defined	yes not defined	66% of the subject presented brain lesions
Critchley[20]	2004	Case Report	Man	yes Right side	Lesions diffused in the brain
Thomke[21]	1997	Prospective	2 men, 1 woman	yes not defined	No identify cablevision in MRI
Fukazawa[22]	1997	Prospective	25 subjects (men *vs.* women: 1: 2.7)	yes not defined	Lesions in the pontine tegmentum ipsilateral to the facial palsy (21 with multi nerve involvement); no lesions in the two with pure facial palsy

stand the origin of the FP.

In two cases (a man and a woman) the authors reported vestibular and auditory symptoms associated with the onset of facial palsy, while another author reported a woman that showed only vertigo complicating his facial paralysis.

In only 1 case, as reported by Kwon et al[18], the origin of facial palsy may be directly correlated with the presence of a lesion in the roof entry zone (REZ).

Overall, none of the authors reported cases of FP linkable with a peripheral demyelination process as for example an involvement of the facial nerve external to the stylus-mastoid foramen, where the nerve comes out from the fallopian canal.

It is also important to remember that a peripheral demyelination in MS patients is rarely described[5] and the most of the authors believe that the motor disease observed in MS is related to the lesion in brain, pons, and medulla more than a peripheral involvement.

In case of MS-related vestibule-cochlear involvement, instead, a peripheral involvement of inner ear might happen[4] in fact the presence of macrophages/microglia has been identified in patients affected from auto-immune diseases in human temporal bone study.[6]

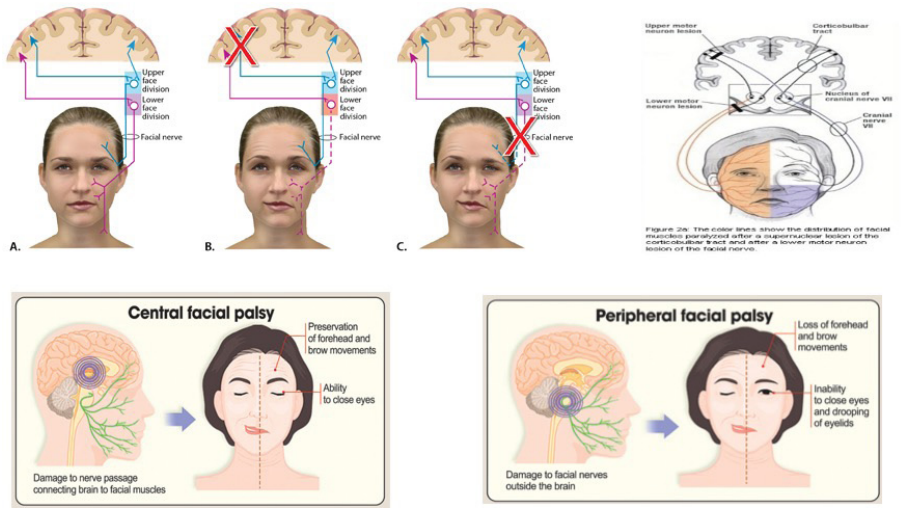
We are trying to understand the reason which, in presence of a MS-related facial palsy, the central lesion mimics a peripheral involvement presenting with a complete involvement of all facial muscles.

Is it possible the majority of the lesions are located in the medulla or, the lesion in the central pathway are associated with a peripheral involvement of facial nerve in its bone tract that is not visible in the magnetic resonance imaging (MRI)?

The particular anatomy of the facial pathway supports the hypothesis of the central involvement, in fact, both cerebral hemispheres (area of motor cortex with the posterior limb of internal capsule and the corticobulbar tract) are responsible for the movement of the frontalis muscle, while only the contralateral cortex innervates the lower motor neurons that drive the muscles under the frontalis. So, due to the wide diffusion of MS lesions in the brain, is very uncommon to observe the typical "central facial palsy" in those patients (Figure 2), while is more common to observe a "peripheral facial palsy".

The action of the microglia supports the concept of superior facial pathway involvement in the MS-related facial palsy, in fact, these cells (responsible of demyelization phenomena) are

Figure 2. *The Image Illustrates the Differences between a Central Facial Palsy with Normal Frontalis Muscle Movement and a Peripheral Form in which all Muscles are Affected from Paralysis*



commonly found in the brain and they may migrate in other structures, as for example the inner ear, but they are rarely identified in peripheral nerves when they come out from their bone tract.

The involvement of facial nerve may be plausible in the internal auditory canal (IAC) but an attack of microglia outside this area is very improbable; furthermore, by reviewing the literature none of the authors reported lesion in the IAC in patients affected from FP so, we could deduct that the central lesions only, are responsible for the onset of facial disease.

We may conclude that the central facial pathway is responsible for the manifestations of MS-related facial paralysis.

In our opinion, additional studies are needed to evaluate the prevalence of peripheral *versus* central involvement in MS-related facial palsy, and to shed light on its pathophysiology.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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None.

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