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WHEN MS DOESN'T GIVE ANOTHER CHANCE: ABOUT 3 AGGRESSIVE CASES

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INTRODUCTION

➢Multiple sclerosis (MS) is a demyelinating disease that attacks specifically the central nervous system. The prevalence around the world knows a heterogenous distribution with a high prevalence in Europe and North America

➢In Africa, the prevalence is more likely to be important in North Africa and less important in Sub-Saharian Africa. We report three observations about Moroccan patients with a highly aggressive progressive MS and discuss risk factors in each patient and in our population

OBSERVATIONS

➢ First patient: **Mrs. TB:**

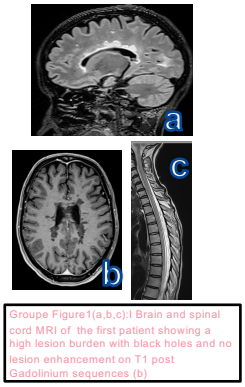
- **49** YO, No personal nor familial medical history.
- **2019:** left lower limb paresis
- **2020:** Right lower limb paresis + Acute urine retention
- **January 2021:** Action tremor of both arms + Cerebellar dysarthria
- **April 2021:** Acute transverse myelitis + cerebellar ataxia
- **Admission:** EDSS at 6
- **MRI: Groupe figures 1**
- **CSF study:** Oligoclonal bands Profile Type 2
- Negative autoimmune and infectious investigations
- **Diagnosis:** Active Progressive MS
- **Treatment:** 5 g of Methylprednisolone + Cyclophosphamide 1g per month for 6 months then evaluate the response to treatment to decide about maintenance treatment.
- **Evolution:** Slight improvement in her lower limbs strength after 5 g of Corticosteroids

➢ Second patient: **Mr. MT:**

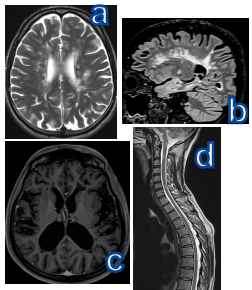
- **37** YO, No medical history
- **6 years before admission : presented progressively over 1 year :**
  - **Left Limb Paresis**
  - **Cerebellar ataxia**
  - **Urinary Urgency**
  - **Walking distance reduced to 500m**
- **Physical examination:**
  - **Partial Myelitis**
  - **Cerebellar ataxia in 4 limbs**
  - **Left Trigeminal Hypoesthesia**
  - **MMSE: 29/30. MoCA: 20/30**
  - **EDSS: 4.5**
- **MRI: Groupe figures 2**
- **Treatment: 3 g of Methylprednisolone**
- **Evolution: no improvement**

➢ Third patient: **Mrs. HZ:**

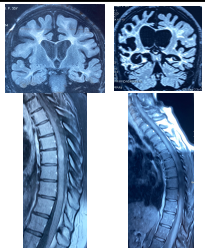
- **35** YO, college graduated
- **2013:** Epileptic seizures resistant to antiepileptic drugs + Left Hemiparesis ➔ First brain and spinal MRIs and paraclinical investigations: progressive MS
- **2021:** Spastic hemiparesis+ Aggressive + Dementia + MMSE: 12/30 + **EDSS at 8**
- **MRI: Groupe figures 3**
- **Treatment: 3 g of Methylprednisolone**
- **Evolution: no improvement**



Groupe Figure1(a,b,c):I Brain and spinal cord MRI of the first patient showing a high lesion burden with black holes and no lesion enhancement on T1 post Gadolinium sequences (b)



Groupe figures 2 (a,b,c): a: Brain MRI T2 weighted image showing hyperintensities surrounging the ventricles. B: Brain MRI FLAIR-weighted image showing dawson fingers aspect. C: Brain MRI T1 post Gadolinium sequence showing no lesion enhancement. D: Spinal cord MRI T2 wieghted sequence showing 3 hyperintensities not extensive.



Groupe figure 3: Brain FLAIR weighted images 2019 (left) 2021(right). Spinal cord T1 weighted images 2019 (left) 2021 (right) showing continued atrophy process in this patient.

DISCUSSION

➢Common risk factor for our patients:

- **African origin :** The first study which evoked the aggressivity of the North African MS phenotype was enrolled in Nice (Jeannin et al, Rev Neurol 2006). Patients of African descent requiring a cane were 2.2 to 2.8 times more than whites. Araqi-Houssaini et al published a multicentric study about severity of MS in Morocco, and their results were consistent with those published earlier about african migrants to Europe with more fast and malignant forms of MS (Araqi-Houssaini et al, Multiple sclerosis 2014). Kallenbach Aurenção et al were interested in reviewing the literature about afro-descendant being a risk factor for disability and severe progression of the disease. Some interesting data was taken, as the severe relapses with short time between relapses and the higher disability scires (Kallenbach Aurenção et al, Arq Neuropsiquiatr. 2016).
- **Age of onset:** > 50 YO increases the handicap risk by 2 compared to an onset at 20 YO. Every decade worsens the EDSS by 0,43 . Patients who start their MS after 45 YO use a cane 5 years later
- **Clinical presentation:** incomplete recovery after relapses increases the handicap risk by 10. Type of relapses: myelitis, cerebellar, sphincter disorders and cognitive impairment are associated to bad prognosis
- **Radiological factors:** an important lesion burden on T2, black holes on T1, Brain atrophy, Brainstem and spinal cord lesions are attached to a higher handicap compared to those with less important lesions on MRI.
- **CSF characteristics:** Oligoclonal bands increase the handicap risk by almost 50%.

➢Other possible factors:

- **Genetic factors: HLA-DRB1*15:** Ouadghiri et al, studied the HLA-DRB1 allele frequencies in Moroccan patients with MS and proved a positive association with the HLA-DRB1-15 as a genetic predisposition to MS (Ouadghiri et al, Pathol Biol, 2013). This same powerful gene, which is epigenetically regulated, was attached to immune changes, as in HLA-DR1-15 positive patients the Th1 lymphocytes auto-proliferate in an elevated way and it may allow binding and presentation of CNS antigens to T cells (Waubant et al, Ann Clin Transl Neurol. 2019).
- **Vitamin D serum level:** many of the reported therapeutic essays of vitamin D supplementation for people with MS have had limitations of small sample size (low power), short duration, and including patients who are not deficient vitamin D and still mostly don't prove any efficacy on the EDSS score or annual relapses rate (Feige et al, Nutrients. 2020, Smolders et al, CNS Drugs. 2019). Despite a sunny climate, the north African region has a high prevalence of vitamin D deficiency which was confirmed by a study carried out by our team and no significant correlation between vitamin D deficiency and the evolution of MS was observed (Skalli et al, Rev Neurol 2018). Seasonal differences in MS activity have also been reported. The predicted correlation between sun exposure and increased levels of vitamin D would suggest higher disease activity during low sun exposure seasons such as fall and winter {Rosecrans, 2014 #134}. However, recent studies have rather suggested the opposite, namely that disease activity increases during spring and summer {Spelman et al, 2014}.
- **Obesity**: Obesity is a low-grade inflammatory condition and may act as a pro-inflammatory cofactor leading to earlier onset of age and more aggressive inflammation in MS
- **Diet:** A diet high in salt would have a pro-inflammatory effect on animal models. This has not been confirmed in humans too.
- **Infections:** In genetically MS predisposed individuals, studies have shown that microbial infections can act as environmental triggers in inducing or promoting the onset of clinical signs of MS (Christen, et al, 2005). Furthermore, studies conducted in the developed countries have shown that people who were exposed to a higher level of sanitation during childhood had a higher risk of developing MS in adulthood (Bach et al, 2002)
- **Lifestyle risk factors:** Both active and passive tobacco smoking has been highly associated with MS onset with a clear dose-dependent relationship

CONCLUSION

Aggressive primary progressive MS is a real diagnostic and therapeutic challenge. Our patients had different presentation forms but all of them quickly climbed their EDSS in a short time. There are several risk factors in Africa and the first one is being of non-white race. Vitamin D deficiency, Genetic factors and poor-quality diet are other risk factors that we discussed through those observations.