

# **RESEARCH ARTICLE**

## NEUROFIBROMATOSIS TYPE 1 IN MULTIPLE SCLEROSIS IN SAUDI ARABIA: CASE REPORT AND LITERATURE REVIEW

# Kawther Hadhiah<sup>1</sup>, Abdulla Al-Fajri<sup>2</sup>, Hassan Ali Al-Dandan<sup>1</sup> and Jumana Al-Atiya<sup>3</sup>

.....

- 1. Department of Neurology in Imam Abdulrahman Bin Faisal University, King Fahd Hospital of University, Al-Khobar, Saudi Arabia.
- 2. Department of Internal Medicine ,Neurology Unit in King Salman Hospital-Riyadh, Ministry of Health.Saud Arabia.
- 3. College of Medicine, King Faisal University. Al-Hassa, Saudi Arabia.

## Manuscript Info

#### Abstract

*Manuscript History* Received: 25 March 2021 Final Accepted: 29 April 2021 Published: May 2021

#### Key words:-

Multiple Sclerosis (MS), Neurofibromatosis Type 1(NF1), Relapsing Remitting (RRMS), Adult, Saudi Arabia, Fingolimod **Background:** Neurofibromatosis type I(NF1) is a neurocutaneous autosomal dominant disorder that has variable skin and neurological manifestation and Multiple sclerosis (MS) is not among these neurological sequalae of Neurofibromatosis. Only 26 cases have been reported worldwide to have the combination of these two neurological diseases, and none of them from Saudi Arabia. We are presenting a young lady who was diagnosed to have Multiple Sclerosis, Relapsing remitting form as she is fitting the clinical and the radiological criteria, and by the age of 29 years, she was thoroughly investigated for multiple café au lait spot lesions in the trunk and neurofibromas and history of childhood seizures.

**Case Presentation:**29-year-old lady who was diagnosed to have Relapsing- Remitting Multiple Sclerosis (RRMS) 7 years ago as she is fulfilling the clinical and radiological criteria of Multiple sclerosis and maintained on Interferon beta 1a 44 mcg subcutaneous every other day then shifted to Fingolimod. Upon encountering her in the clinic, there were multiple café au lait spot lesions in the trunk and neurofibromas. Genetic testing showed pathogenic nonsense variant c.574C>T p.(Arg192\*) in exon 5 of the NF1 gene.

**Conclusion:**Relapsing remitting form of multiple sclerosis (RRMS) can be associated with Neurofibromatosis type 1(NF1), not only progressive form and NF1 can be related to spontaneous mutation in 50% of cases (no family history).

Copy Right, IJAR, 2021,. All rights reserved.

**Introduction:-**

Neurofibromatosis type I is a neurocutaneous autosomal dominant disorder caused by gene mutation located on long arm chromosome 17 segment 17q11.2 which encodes a protein calledneurofibromin <sup>(1)</sup>with an incidence around 1 in 2500 to 3000 persons<sup>(2)</sup>without clear epidemiological data from Saudi Arabia. The disease can be manifested with café-au-laitspots, neurofibromatosis, inguinal/axillaryfreckles andLisch nodules <sup>(2)</sup>, along with neurological sequalae such as optic gliomas, epilepsy, peripheral nerve sheath tumor and lacunar stroke <sup>(3)</sup>. Multiple sclerosis is the most prevalent progressive demyelinating immune- mediated inflammatory disorder of the brain and

#### **Corresponding Author:- Kawther Hadhiah**

Address:- Department of Neurology in Imam Abdulrahman Bin Faisal University, King Fahd Hospital of University. Al-Khobar, Saudi Arabia.

spinal cord <sup>(4)</sup>. The prevalence of multiple sclerosis in Saudi population is 61.95/100,000 and more common among young, educated and females<sup>(5)</sup>. we are reporting the first case in Saudi Arabia with Neurofibromatosis type 1 and multiple sclerosis. On the other hands there are few cases have been reported in the literature <sup>(2)</sup>. Little is known about patients who have this combination of disorders and further studies need to be established for better management with possible genetic therapy and to find out further genetic correlation of both diseases.

## **Case Presentation**

29 years-old female known case of relapsing-remitting Multiple Sclerosis for 7 years. She was in her usual state of health (fully independent) until 2 days before visiting emergency department at King Fahd Hospital of University in Al-Khober complaining of walking difficulty, left lower limb weakness and numbness. It was progressive over 2 days and exacerbated by exercise and heat exposure. There was no history of fever, visual symptoms, bulbar symptoms, weight loss, headache, vertigo, sphincter involvement, back pain or recent upper respiratory tract infection. No relieving factors. She has similar presentation 1 year back.Medications history include Interferon beta 1a 44 mcg subcutaneous every other day and Vitamin D 1000 International units once daily. Past medical History represents presence of seizures since age of 4 years, generalized tonic clonic semiology and she was on unknown anti-epileptic drug. Patient became seizure free at age of 7 years and anti-epileptic drug was stopped at that time. Frequency of true relapse is 1 attack every other year with motor symptoms. Unremarkable Surgical history. Patient is a product of consanguineous marriage with no family history of similar condition or neurological diseases.She is single and was performing well in school. She is a graduate of college of education with Bachelor degree, living with her family and working as kindergarten teacher.She is non-smoker, non-alcoholic with no special habits. Menstrual history suggestive of regular menses lasting for 5 days.

## **Clinical findings:**

Patient is alert conscious oriented to place, person and time. Skin examination shows multiple café au lait spot lesions in the trunk and multiple (facial, limbs and trunk) neurofibromas (Figure A, B& C) .Neurological examination in regard of language: fluent, coherent with intact naming, writing and reading.Cranial nerves: pupils both equal in size and reactive to light and no Relative Afferent pupillary defect, normal visual acuity, no visual field defects, normal fundus examination, no extra-ocular muscles restriction, no nystagmus, no facial asymmetry, uvula centralized, intact gag reflex and other cranial nerves unremarkable. Motor examination: mild spasticity in lower limbs, power: 3/5 left side, 4/5 right side of lower limbs, reflexes are exaggerated with non-sustained ankle clonus bilaterally. Babinski signs are present bilaterally.Sensory exam: decreased fine touch and pin prick sensation in the left lower limb till the knee. Cerebellar exam: unremarkable.Gait: unable to stand and walk secondary to the weakness.

## Timeline:

She had an episode of acute relapse where she was admitted in the hospital to receive pulse steroid therapy for 5 days then her examination showed improved weakness in which power examination was 4/5 bilaterally. As well as beta 1a interferon was changed to Fingolimod for further control of the disease progression. After changing immune modifying therapy, patient had no new relapses. Her investigations were remarkable for Serum immunoglobulin G: 1064 (700-1600) mg/dl, Cerebrospinal fluid(CSF) analysis : appearance : clear and colorless, Red Blood Cell 0 (<1000)/cu mm, White Blood Cell 0 (0-5) )/cu mm, CSF albumin level: 13.4 (10-30) mg/dl, CSF glucose 79 (40-70) mg/dl, CSF protein : 35 (15-45) mg/dl, CSF oligoclonal bands : bands detected (oligoclonal bands present in CSF and absent in the serum), CSF immunoglobulin G : 41.6 (10-30) mg/dl, CSF aerobic culture : no growth at 48 hours and Repeated serum JC virus titer done in (11/6/2019): 3.71 (positive for JC virus antibodies and other viral serology tests were negative. On the other hand, Neurofibromatosis gene heterozygous likely pathogenic nonsense variant c.574C>T p.(Arg192\*) in exon 5 of the NF1 gene. Magnetic Resonance Image(MRI) of brain and spine with and without contrast (Figure D-I).

#### Therapeutic interventions:

- 1- Methylprednisolone 1 gram (pulse) given for the acute relapse for 5 days
- 2- Interferon 1a shifted to fingolimod 0.5 mg tablet once daily as the disease was progressing.
- 3- Vitamin D 1000 international units daily.
- 4- Physiotherapy.

#### Follow-up and Outcomes:

Patient improved after active relapse with steroid and medication adjustment in term of improved weakness 4/5 bilaterally and she is able to walk independently with 3-6 months follow up. Fingolimod is well tolerated with no event of bradycardia and no macular edema after 2 months by ophthalmological assessment.

The	Expanded	Disability	Status	Scale	(EDSS)	۱.
1110	Enpanaca	Disconney	Status	Dealey	LDDD	

ambulation scoring: 5.5- ambulatory for 100 meter without aids/rest: disability precludes full daily activities.

Functional parts	Score		
Pyramidal	+2 (minimal disability)		
Cerebellar	+2 (mild ataxia)		
Brainstem	0 (normal)		
Sensory	+2 (mild decrease in pain, fine touch in 1 limb)		
Bowel and bladder	+1 (mild bowel retention)		
Visual	0 (normal)		
Cerebral	+1 (mood alteration only)		
Other	0 (normal)		

# **Discussion and Conclusion:-**

The combination of Neurofibromatosis type 1 and multiple sclerosis is very scarce. In fact, very few cases have been reported with neurofibromatosis type 1 and primary progressive multiple sclerosis (Ferner, Hughes, Johnson, et al.1995, Johnson, Ferner, Bobrow, et al.2000, Pál, E., Gömöri, É., and Gáti, I., et al.2001, Etemadifar M. et al.2009, Hemmarin Pipatpajong MD.et al.2011)<sup>(2)</sup>. We are reporting the first case in Saudi Arabia with Neurofibromatosis type 1 and relapsing-remitting form of multiple sclerosis. The diagnosis of NF1 was made according to the clinical criteria suggested by the National Institutes of Health Consensus Development Conference on Neurofibromatosis<sup>(2)</sup>. Also the diagnosis of multiple sclerosis was confirmed by clinical, radiological and cerebrospinal fluid findings of oligoclonal bandsand high IgG index based on Macdonald's criteria 2017<sup>(6)</sup>. The disease course of our patient is relapsing-remitting form of multiple sclerosis which is similar to S.M. Elsayed et al, 2016<sup>(2)</sup> and P Perini et. al,2001<sup>(2)</sup> which are unlike most of the studies reported previously, where primaryprogressive form of multiple sclerosis described in patients with neurofibromatosis type 1 was the most common<sup>(2)</sup>. There are two theories that possibly explain the association of these two conditions. The first hypothesis that explain the association between these two conditions is the presence of mutation in oligodendrocyte myelin glycoproteind(OMgp) gene<sup>(2)</sup>. This gene that is located in the intron of NF1 plays role in myelination of central nervous system and it can be attacked by an autoimmune process causing demyelination. In the same gene there is point mutation that changes glycine to aspartic acid in multiple sclerosispatients<sup>(2)</sup>. One thing against this hypothesis, is this mutation was not found in primary progressive multiple sclerosis patients with NF1<sup>(2)</sup>. The other hypothesis (theory) suggested that out of control Schwann cell proliferation due to absence of suppression gene with NF1 mutation and might lead to uninhibited response of the immune system (autoimmune) to central nervous system myelin in liable patients<sup>(2)</sup>. In conclusion the prevalence of these two neurological diseases concomitantly is very rare. However, we find that Relapsing remitting form of multiple sclerosis can be associated with neurofibromatosis type 1, not only progressive form and most of these patients have no neurological sequalae related to neurofibromatosis type 1. Neurofibromatosis type 1 can be related to spontaneous mutation in 50% of cases (no family history). Whole genome sequencing will help us to understand this association more clearly and will be the key for future gene therapy.

## Abbreviations

NF1: Neurofibromatosis Type 1, MS: Multiple Sclerosis, RRMS: Relapsing Remitting Multiple Sclerosis, CT: Computed tomography; CTA: CT angiography; DSA: Digital subtraction angiography; MRA: Magnetic resonance angiography; MRI: Magnetic resonance imaging

## Declarations

- 1. Acknowledgements Not applicable.
- 2. Ethical approval Not applicable.
- 3. Consent to participateInformed consent was obtained from the patient herself on Feb.2020

- 4. **Authors' contributions** KH, AA and HA: have been involved in doing the work, gathering data and drafting the manuscript or revising it critically for important intellectual content. JA, assisting us in literature review. All authors have read and approved the final manuscript.
- 5. **Funding**This research did not receive any specific grant from funding agencies in the public, commercial, or for-profit sectors.
- 6. Availability of data and materials The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.
- 7. **Consent for publication**A written consent for publication was obtained from the patient including individual details, and images.
- 8. Competing interests The authors declare that they have no conflict of interest.

**Figure Legends** 



Figure A:- Multiple Neurofibromas in different sizes scattered in the lower back of the patient surrounded by café au lait spots.



Figure B:- Large café au lait spot in the right thigh measuring more than 15 mm in size.



Figure C:- Two Neurofibromas of different sizes located in the left forearm.



Figure (D) &(E): (D) T2 flair axial section of the brain showing both centrum semi ovale (D) and periventricular (E) hyper-intense lesions characteristic for multiple sclerosis



Figure (F) &(G):- T2 axial section of the brain showing multiple right pontine (F) and solitary left cerebellar peduncle hyper-intense lesions (G).





Figure (H) & (I):- MRI Short-TI Inversion Recovery in transverse section of the cervical (H) and thoracic (I) spines showing no lesions.

# **References:-**

- Wallace MR, Marchuk DA, Andersen LB, Letcher R, Odeh HM, Saulino AM, Fountain JW, Brereton A, Nicholson J, Mitchell AL. Type 1 neurofibromatosis gene: identification of a large transcript disrupted in three NF1 patients. Science. 1990 Jul 13;249(4965):181-6.
- Elsayed SM, Fahmy N, Gamal R, Wafik M, Zamzam D, Fahmy M, Suelam M. Neurofibromatosis type 1 and multiple sclerosis: Genetically related diseases. Egyptian Journal of Medical Human Genetics. 2017;18(3):295-8.
- 3. Creange A, Zeller J, Rostaing-Rigattieri S, Brugieres P, Degos JD, Revuz J, Wolkenstein P. Neurological complications of neurofibromatosis type 1 in adulthood. Brain. 1999 Mar 1;122(3):473-81.
- 4. Olek MJ, Howard J. Evaluation and diagnosis of multiple sclerosis in adults. Uptodate. 2019.
- 5. AlJumah M, Bunyan R, Al Otaibi H, Al Towaijri G, Karim A, Al Malik Y, Kalakatawi M, Alrajeh S, Al Mejally M, Algahtani H, Almubarak A. Rising prevalence of multiple sclerosis in Saudi Arabia, a descriptive study. BMC neurology. 2020 Dec 1;20(1):49.
- Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, Correale J, Fazekas F, Filippi M, Freedman MS, Fujihara K. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. The Lancet Neurology. 2018 Feb 1;17(2):162-73.