OPEN ACCESS

Saudi Journal of Medicine
Abbreviated Key Title: Saudi J Med
ISSN 2518-3389 (Print) | ISSN 2518-3397 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Case Report

Association of Neurofibromatosis Type 1 and Multiple Sclerosis: A Case Report

Noura Boukricha[1*], Wadii Bnouhanna[1], Mounia Rahmani[1], Maria Benabdeljlil[1], Saadia Aidi[1]

[1]University Hospital, Neurology A and Neuropsychology, Rabat, Morocco

DOI: https://doi.org/10.36348/sjm.2024.v09i08.001 | **Received:** 24.06.2024 | **Accepted:** 01.08.2024 | **Published:** 07.08.2024

***Corresponding Author:** Noura Boukricha
University Hospital, Neurology A and Neuropsychology, Rabat, Morocco

Abstract

Neurofibromatosis type 1 (NF1) is an autosomal dominant neurocutaneous disorder, while multiple sclerosis (MS) is a prevalent chronic inflammatory demyelinating disease of the central nervous system. The coexistence of these two conditions is rare. Thus, patients with NF1 may exhibit signal abnormalities on brain imaging, referred to as focal areas of signal intensity (FASI), which can mimic lesions seen in MS and complicate the differential diagnosis. We present the case of a female patient suffering from progressive paraparesis, accompanied by urinary disorders and coordination disorders of the upper limbs. Neurological examination revealed a pyramidal syndrome and a cerebellar syndrome, with an Expanded Disability Status Scale (EDSS) score of 7.5. Additionally, the skin examination showed multiple café-au-lait spots larger than 15 mm and numerous diffuse neurofibromas. Brain magnetic resonance imaging showed white matter lesions typical of MS, and isoelectrofocalization of cerebrospinal fluid proteins revealed positive oligoclonal bands. The diagnosis was primary progressive multiple sclerosis associated with neurofibromatosis type 1. The aim of this case report is to document the association of these two conditions and discuss the challenges in differential diagnosis and treatment, as early diagnosis of MS is crucial to prevent further disability in patients with NF1.

Keywords: Neurofibromatosis type 1; Multiple Sclerosis; MRI; FASI.

INTRODUCTION

Neurofibromatosis type 1 (NF1) or Von Recklinghausen disease is an autosomal dominant disorder caused by mutations in the NF1 gene, which encodes for the tumor suppressor protein neurofibromin [1]. It is recognized as a heterogeneous neurocutaneous syndrome, manifesting with café-au-lait spots, Lisch nodules on the iris, freckles in the axillary and inguinal regions, bone lesions, as well as various neurofibromas [2, 3]. The neurological manifestations of NF1 include mild intellectual impairment, epilepsy, macrocephaly, optic nerve and parenchymal gliomas [3, 4]. Multiple sclerosis (MS) is a common immune-mediated inflammatory disease that leads to chronic demyelination of the central nervous system. Although rare, the association between these two conditions has been documented in the literature, with fewer than 20 cases described in PubMed. We report the case of a woman with NF1, presenting with a clinical and imaging picture consistent with primary progressive MS (PPMS). This case report focuses on the radiological aspects and therapeutic challenges present in these patients.

CASE PRESENTATION

We describe the case of a 45-year-old woman diagnosed with MS and NF1. The patient had a son with skin lesions characteristic of NF1. She presented with progressive lower limb weakness, gait and balance disturbances evolving over 3 years, associated with urinary incontinence and coordination disorders of the upper limbs.

The neurological examination revealed spastic tetraparesis, more pronounced in the lower limbs, which made walking and standing impossible. The patient also exhibited generalized hyperreflexia, bilateral Babinski signs, and bilateral kinetic cerebellar syndrome. The Expanded Disability Status Scale (EDSS) score was 7.5. The ophthalmological examination was normal. Skin examination showed multiple lesions characteristics of NF1; including multiple café-au-lait spots larger than 15 mm and multiple diffuse neurofibromas all over the body, involving the face and scalp, appearing at the age of puberty (Figure 1).

Brain magnetic resonance imaging (MRI) revealed multiple hyperintense lesions on T2 and fluid-attenuated inversion recovery (FLAIR) sequences. The lesions were primarily located in the periventricular regions, displaying an ovoid shape and oriented perpendicular to the ventricular axis. They also involved the brainstem and cerebellar peduncles (Figure 2). These lesions did not show enhancement after gadolinium administration, and some were noted as black holes on T1-weighted images. The spinal MRI was normal.

Visual evoked potentials were bilaterally impaired, indicating subclinical involvement of the optic nerves. Lumbar puncture and cerebrospinal fluid (CSF) analysis revealed a leukocyte count of 40, normal glucose levels (0.56 g/L), and normal protein levels (0.41 g/L). Isoelectrofocusing of CSF proteins showed positive oligoclonal bands (OCB) and intrathecal synthesis of type 2. Immunological assessment and other biological tests were normal. X-ray of the lower limbs revealed no signs of bone malignancy. The diagnosis of primary progressive multiple sclerosis (PPMS) was established based on the 2017 Revised McDonald Criteria, in association with neurofibromatosis type 1 (NF1), as the patient exhibited skin signs meeting the National Institutes of Health (NIH) diagnostic criteria for NF1.

Given that our patient has non-active primary progressive multiple sclerosis (PPMS) with an EDSS of 7.5, and considering the cancer risk associated with disease-modifying therapies (DMTs), the chosen treatment approach involved symptomatic management of spasticity while abstaining from DMTs.

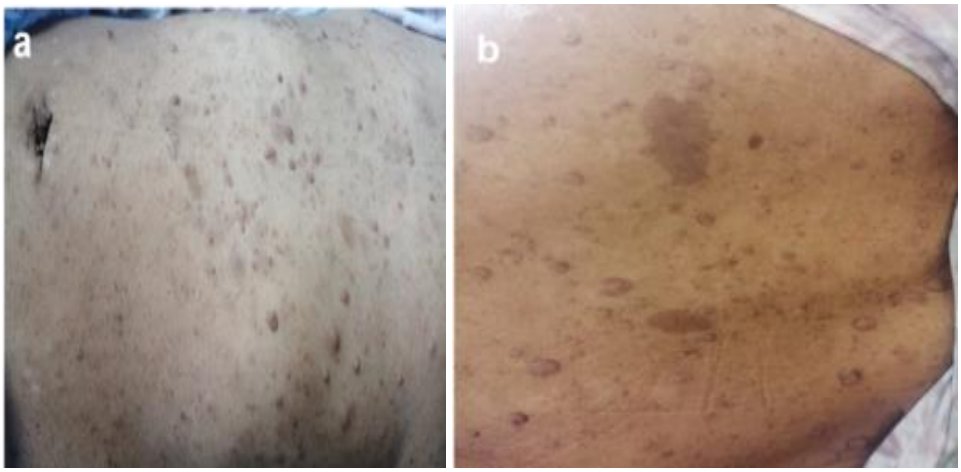
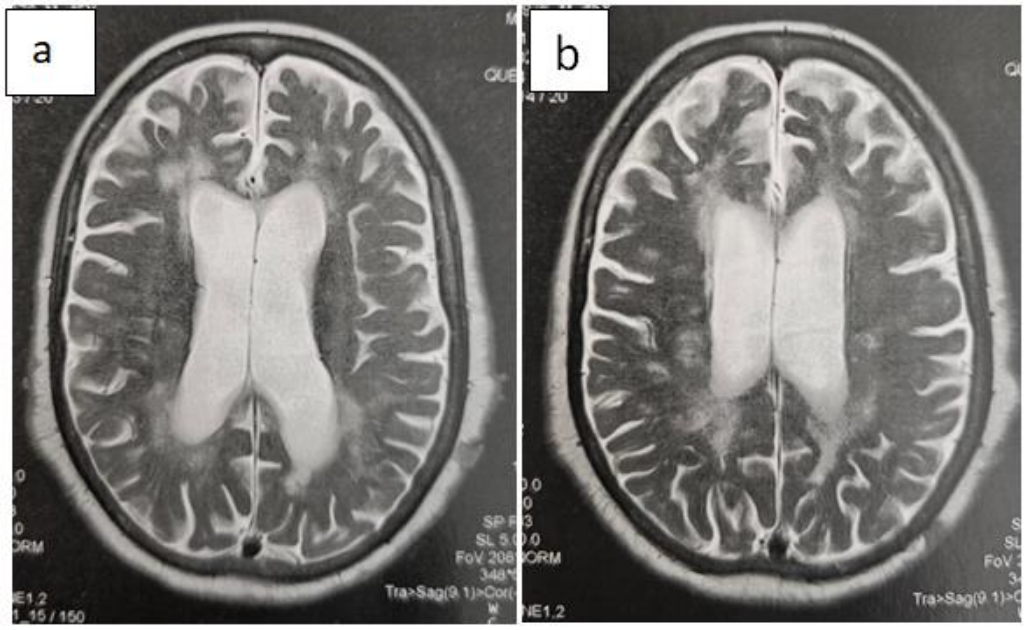


Figure 1: Café-au-lait spots and multiple neurofibromas on the abdomen (a) and back (b)



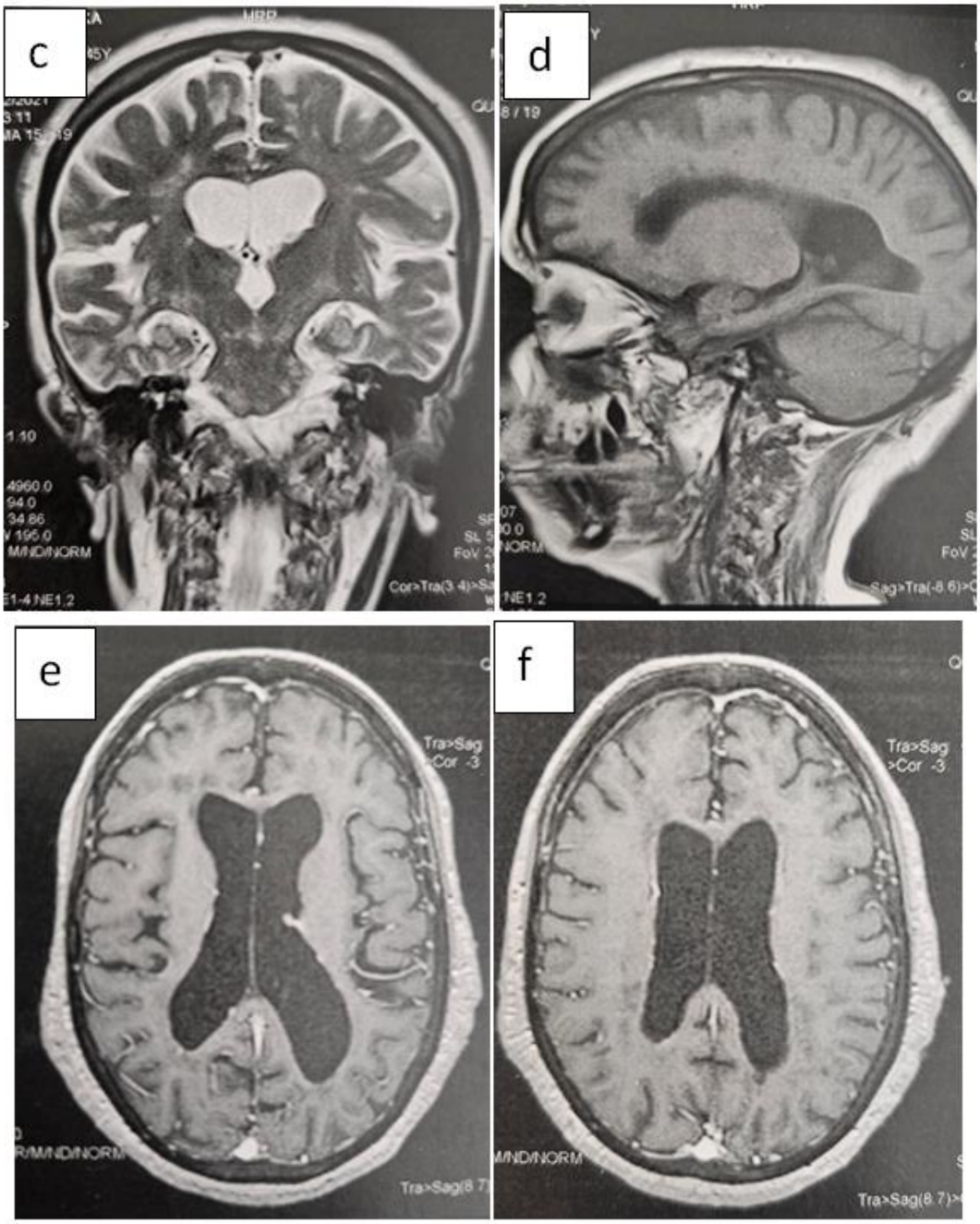


Figure 2: Brain MRI showing multiple hyperintensities on T2-weighted images, predominantly in the periventricular regions (a, b) and brainstem (c), with corresponding hypointensities on T1-weighted images (d), and no enhancement after gadolinium injection (e, f)

DISCUSSION

Although rare, the coexistence of MS and NF1 has been reported in the literature, with studies suggesting a genetic link between the two conditions and an increased risk of developing MS in patients with NF1 [5]. In our case study, we report the case of a patient who initially presented with cutaneous signs fulfilling the NIH diagnostic criteria for NF1 (multiple café-au-lait spots over 15 mm with multiple diffuse neurofibromas) [7] and was later diagnosed with PPMS, the most common form of MS in NF1 patients, based on clinicoradiological features and CSF findings.

Patients with NF1 can present with signal abnormalities on brain imaging, called focal areas of signal intensity (FASI), which have no clinical consequences. These abnormalities may resemble the lesions of MS, but there are certain features that differentiate them. Firstly, although both FASI and MS lesions present as T2 hyperintensities, MS lesions appear as T1 hypointensities, while FASI lesions are T1 isointense. Secondly, localization and enhancement can also be useful indicators for differentiating FASI and MS lesions. FASI typically occur in the basal ganglia, brainstem, and cerebellum, and usually do not enhance,

except in rare cases where they show focal enhancement. In contrast, MS lesions are typically located in the corpus callosum, periventricular, or cortical/juxtacortical areas and present an oval morphology. Moreover, MS lesions may enhance after gadolinium administration. Finally, lesion size and progression may also help in differentiation. MS lesions are known to evolve over time, varying in size, number, location, and enhancement pattern, reflecting their inflammatory activity. In contrast, FASI are often larger than MS lesions, tend to grow slowly before stabilizing around age 10 [7-10]. Nevertheless, there are overlaps and exceptions in terms of lesion location, enhancement, and signal intensity, making differentiation particularly challenging. According to the MAGNIMS criteria [7], our patient presented with periventricular and brainstem lesions typical of MS. In contrast, MRI did not show any lesions related to NF1.

The treatment of MS relies on immunosuppression, which may elevate the risk of malignancy, particularly in the presence of a tumor-predisposing condition like NF1. Clinicians must therefore carefully weigh the risk of cancer associated with DMTs against the prevention of neurological disability in patients diagnosed with both conditions. Currently, there are no established guidelines for managing these patients, partly due to the rarity of the coexistence of the two pathologies and the limited data on the oncogenic risk of MS therapies. This significantly complicates the task for clinicians [9, 11].

CONCLUSION

The association between MS and NF1, although very rare, requires attention due to the diagnostic and therapeutic challenges it poses. On one hand, the clinical and radiological neurological manifestations of MS and those associated with potential complications of NF1 may exhibit similarities, often leading to delays in the diagnosis of MS. Therefore, a thorough neurological evaluation of NF1 patients presenting with new or unusual clinical symptoms, along with accurate interpretation of complementary examinations, is crucial, as early diagnosis and treatment of MS can improve prognosis and prevent further disability. On the other hand, managing these cases presents challenges for clinicians, as no guidelines have been developed to date. Case reports, such as the one presented, can contribute to the development of appropriate diagnostic criteria and therapeutic strategies in patients with NF1 and MS.

REFERENCES

1. Reynolds, R. M., Browning, G. G. P., Nawroz, I., & Campbell, I. V. (2003). Von Recklinghausen's neurofibromatosis: neurofibromatosis type 1. *The lancet*, *361*(9368), 1552-1554.
2. Iwanowski, P., Kowalska, M., Prendecki, M., Dorszewska, J., Kozubski, W., Rydzanicz, M., ... & Losy, J. (2019). Primary progressive multiple sclerosis and neurofibromatosis type 1. *Multiple Sclerosis and Related Disorders*, *32*, 66-69. doi: 10.1016/j.msard.2019.04.016
3. Perini, P., & Gallo, P. (2001). The range of multiple sclerosis associated with neurofibromatosis type 1. *Journal of Neurology, Neurosurgery & Psychiatry*, *71*(5), 679-681. 10.1136/jnnp.71.5.679
4. Mohebi, N., Moghaddasi, M., & Maryam, Z. (2015). Relapsing remitting multiple sclerosis in an Iranian patient with neurofibromatosis type I. *Neurology International*, *7*(2), 5966.10.4081/ni.2015.5966
5. Elsayed, S. M., Fahmy, N., Gamal, R., Wafik, M., Zamzam, D., Fahmy, M., & Suelam, M. (2017). Neurofibromatosis type 1 and multiple sclerosis: genetically related diseases. *Egyptian Journal of Medical Human Genetics*, *18*(3), 295-298.
6. (1988). Neurofibromatosis: Conference Statement. *Arch Neurol*, *45*(5), 575–578.
7. Filippi, M., Rocca, M. A., Ciccarelli, O., De Stefano, N., Evangelou, N., Kappos, L., ... & Barkhof, F. (2016). MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines. *The Lancet Neurology*, *15*(3), 292-303.
8. Carvalho, I., Quintas-Neves, M., Pinto, J., Santos, A. F., & Pereira, J. (2021). Primary progressive multiple sclerosis in a portuguese patient with neurofibromatosis type 1. *Cureus*, *13*(12), e20561.
9. Lemonaris, M., & Kleopa, K. A. (2024). Highly Active Relapsing-Remitting Multiple Sclerosis with Neurofibromatosis Type 1: Radiological Aspects and Therapeutic Challenges–Case Report. *Case Reports in Neurology*, *16*(1), 48-54.
10. Russo, C., Russo, C., Cascone, D., Mazio, F., Santoro, C., Covelli, E. M., & Cinalli, G. (2021). Non-oncological neuroradiological manifestations in NF1 and their clinical implications. *Cancers*, *13*(8), 1831.
11. Melamed, E., & Lee, M. W. (2020). Multiple sclerosis and cancer: the ying-yang effect of disease modifying therapies. *Frontiers in immunology*, *10*, 2954.