

Coexistence of neurofibromatosis type I, multiple sclerosis, and ischemic stroke: A case report and literature review

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Abstract

Neurofibromatosis type I and multiple sclerosis, when considered separately, are associated with a higher risk of cerebrovascular accident. The coexistence of neurofibromatosis type I and multiple sclerosis may lead to a further increase in cerebrovascular risk; however, this has not been reported in the literature. We report the case of a 37-year-old woman affected by both neurofibromatosis type I and multiple sclerosis: she was referred to our rehabilitation department because of a recent event of ischemic stroke. Moreover, we provide a comprehensive and updated review of all published cases reporting the coexistence of neurofibromatosis type I and multiple sclerosis to gather information regarding their association with cerebrovascular accidents.

Keywords

Multiple sclerosis, neurofibromatosis, stroke

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Introduction

Neurofibromatosis type I (NF-1) is a rare complex multisystem human disorder caused by the mutation of a gene on chromosome 17 responsible for neurofibromin production, a protein that is needed for normal function in many human cell types, including neurons.¹ Multiple sclerosis (MS) is the most frequent demyelinating disease affecting young people; characterized by widespread myelin damage and neurodegeneration in the brain and spinal cord.² Cerebrovascular accidents (CA) encompass a variety of medical conditions that affect cerebral perfusion or vasculature.³ These three pathologies cause functional impairment and disability.

Compared to the general population, the odds of any type of stroke are increased in both adult and pediatric patients with NF-1.⁴ It has not been reported whether the coexistence of NF-1 and MS possibly determines a further increase in cerebrovascular risk.

We report the case of a 37-year-old woman suffering from NF-1, MS, and a recent ischemic stroke. Moreover, we provide a comprehensive and updated review of all published cases reporting the coexistence of NF-1 and MS to gather information on their association with CA.

Case report

A 37-year-old woman with both NF-1 and MS was referred to our rehabilitation department because of a recent ischemic stroke.

The patient's neurological history began at the age of 19: NF-1 was diagnosed after the removal of a plexiform neurofibroma in the right foot; a glioma of the left optic nerve and café au lait macules were also detected. No genetic confirmation of the NF1 was performed.

Ten years later, she underwent a neurological reevaluation due to the onset of balance impairment, gait ataxia, and mild paresis of the left lower limb. Brain and spinal cord magnetic resonance imaging (MRI) revealed several demyelinating

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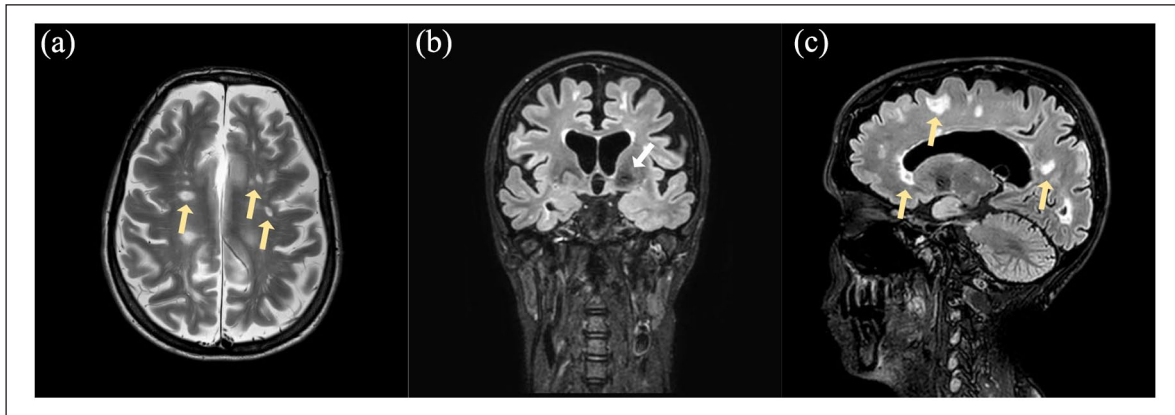


Figure 1. (a) Axial T2 brain MRI showing multiple white matter inflammatory lesions. (b) Coronal brain MRI showing hypodensities in the left thalamus. (c) Sagittal brain MRI showing multiple white matter inflammatory lesions.

Table 1. Most evident progressive improvements in balance control, stride length, and walking speed were recorded during the first 5 months after the stroke.

Month/year	January 18	March 18	May 18	January 19	February 20	January 21
Evaluation time	T0	T1	T2	T3	T4	T5
modified-Clinical Test for Sensory Interaction on Balance-Smart Balance Master-Natus.com	NP	2.3	1.9	1.9	2.30	2.1
Step length	0.43	0.49	0.6	0.57	0.62	0.58
Velocity	0.63	0.87	1.18	1.17	1.14	1.21
Walk ratio: mm/(steps/min) normalized for height	4.89	4.60	5.08	4.63	5.62	4.63
modified-Fatigue Impact Scale (m-FIS) ^a	NE	32/84	25/84	17/84	18/84	13/84
Functional Independence Measure (FIM) ^b	96	120/126	120/126	120/126	120/126	120/126

NP: not performed.

^aFor m-FIS: the higher the score, the worse the fatigue.

^bFor Equiscale and FIM: the higher the score, the better the performance.

lesions (left *thalamus*, right *pallidus*, and spinal lesions at C2, C4, and C5; Figure 1), visual evoked potentials showed a marked increase in latency and cerebrospinal fluid (CSF) was positive for oligoclonal bands. Clinical history, imaging, and CSF were suggestive of relapsing-remitting MS.⁵ An immunomodulatory treatment with teriflunomide was then introduced.

Over time, the patient also developed hypertension and dyslipidemia, known risk factors for stroke.

No family history of stroke, smoking, atrial fibrillation, and/or atrial heart disease were reported.

At the age of 37 years, the patient was referred to the emergency room because of the sudden onset of right upper limb paresis, speech and swallowing impairment, and gait ataxia. The first computed tomography scan excluded hemorrhagic lesions. The acute clinical presentation suggested a cerebrovascular event rather than an MS *poussée*, and the patient underwent systemic thrombolysis with partial benefit (NIHSS 3 at the end of the treatment). Subsequent MRI showed recent hypointense lesions in the thalamus and internal capsule of the left hemisphere and in the lenticular nucleus of the right hemisphere, suggestive of a recent ischemic stroke (Figure 1).

Ten days after the stroke, the patient was transferred to our post-acute rehabilitation facility due to left-sided hemiparesis, balance impairment, speech, and swallowing disorders. Functional follow-up was conducted up to 3 years after the stroke.

The most evident improvements in balance control, stride length, and walking speed were recorded during the first 5 months after the stroke. The patient's functioning remained stable at follow-up visits performed 1 and 2 years later (Table 1).

We conducted a literature review following the PRISMA guidelines. The study population consisted of patients with a confirmed diagnosis of MS and clinical NF1. We searched the following databases for relevant studies: PubMed, Medscape, and Embase. Since NF-1 is a rare disease, we also searched the *Orphanet Journal of Rare Diseases*. Original articles were included, despite the language of publication.

The diagnostic criteria for NF1 are met in an individual who does not have a parent diagnosed with NF1 if two or more of the following are present: six or more café-au-lait macules over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in postpubertal

individuals, freckling in the axillary or inguinal region, two or more neurofibromas of any type or one plexiform neurofibroma, optic pathway glioma, two or more iris Lisch nodules identified by slit lamp examination or two or more choroidal abnormalities, a distinctive osseous lesions such as sphenoid dysplasia, anterolateral bowing of the tibia, or pseudarthrosis of a long bone, a heterozygous pathogenic NF1 variant with a variant allele fraction of 50% in apparently normal tissue such as white blood cells.⁶

Differential MRI features between MS lesions and Focal Areas of Signal Intensity (FASIs) of NF1 are summarized in Table 2.

The selected studies included 42 patients (23 women, 11 men, and 8 unspecified). The main inclusion criteria were a confirmed diagnosis of NF1 and MS ($n=14$ primary progressive (PPMS), $n=8$ secondary progressive (SPMS), $n=13$ relapsing remitting (RRMS), $n=1$ progressive, $n=6$ unspecified). Only eight patients were followed longitudinally for a

Table 2. Differences in the NMR of MS lesions from FASIs in NF1.

Site and NMR sequences	MS	NF1
Site	Periventricular region	Basal ganglia (often the globus pallidus), thalamus, brainstem (pons), cerebellum, and subcortical white matter
T1	Hypointense ("black hole")	Isointense to hyperintense
T2 FLAIR	Hyperintense Hyperintense	Hyperintense Hyperintense

FASIs: focal areas of signal intensity, MS: multiple sclerosis; NF-1: neurofibromatosis type I.

period ranging from 1 year to 20 years. In all, 41 out of 42 patients fulfilled the diagnostic criteria for NF1. Genetic data were reported in four papers (Table 3).

An American administrative claims analysis reported 25 cases of MS among the 8552 subjects affected by NF-1: no clinical and/or genetic information was available for these patients; therefore, we excluded them from the subsequent review.¹¹

Only one study out of 23 reported two cases of CA: a 42-year-old woman with a hemorrhagic lesion in the right posterior limb of the internal capsule¹² and a 62-year-old woman who died due to ruptured brain aneurysm (Table 4).¹²

Discussion

We reported an uncommon case of a patient affected by NF1, MS, and ischemic stroke. Including our patient, only 43 cases of coexisting NF-1 and MS have been reported in the literature, of which three cases of associated NF-1, MS, and CA.

The coexistence of NF-1 with MS has been reported to be more common in the primary progressive form than in the relapsing-remitting form.²⁰

From a rehabilitation perspective, patients with NF-1 and MS face a progressive functional worsening, which current treatments can only counteract for a short period. Differently, CA-related impairment and disabilities, if properly and timely treated³⁰ in the post-acute phase, improve and stabilize over time, as seen in this case.

According to existing literature, treatment with subcutaneous interferon beta 1a (IFN- β 1a) does not increase the risk of stroke in patients with MS.³¹ Muhannad et al. reported a case of alemtuzumab-induced simultaneous onset of autoimmune hemolytic anemia, alveolar hemorrhage, nephropathy, and stroke in a 52-year-old man that occurred 8 months after treatment initiation.³² On the other hand, dimethyl fumarate

Table 3. Genetic data.

No.	Authors	Year	Patients (n)	Other information
1	Carvalho et al. ⁷	2021	1	The genetic study revealed the following heterozygous mutation in the NF1 gene, c.888+1G>T. Although this genetic variant has not been published in the literature, other single nucleotide substitutions (G>A and G>C) in the same position have already been described and considered pathogenic due to splice donor site
2	Piotr Iwanowski ⁸	2019	1	We reported a novel de novo c.6817delC deletion and rs1801052 polymorphism in the NF1 gene associated with NF1 symptoms, as well as numerous polymorphisms in SPG7, SPG15, and SPG39 genes responsible for benign spastic paraplegia.
3	Pipatpajong et al. ⁹	2011	1	The association (between MS and NF) has been hypothesized to be related to mutations in the neurofibromin protein or oligodendrocyte-myelin glycoprotein (OMgp) gene
4	Johnson et al. ¹⁰	2000	0	The DNA from two patients was found to contain an alteration in the OMgp gene resulting in an amino acid change in glycine to aspartic acid at codon 21. It is concluded that PPMS in patients with NF1 can occur without concurrent mutation of the OMgp gene. The glycine to aspartic acid polymorphic alteration at codon 21 is neither sufficient nor necessary for the development of PPMS.

MS: multiple sclerosis; NF-1: neurofibromatosis type I; PPMS: primary progressive.

Table 4. Literature selection for the synthesis of results.

No.	Authors	Year	Patients (n)	Age at MS onset, years	Sex	Type of MS	NFI	Stroke	Follow-up	Other information
1	Ciotti et al. ¹³	2021	1	31	M	RR	NFI			
2	Virgilio et al. ¹⁴	2021	1	55	M	PP	NFI			
3	Carvalho et al. ⁷	2021	1	25	M	PP	NFI			Genetic aspects
4	Bergqvist. ¹⁵	2020	1	45 (mean)	NS	RR	NFI			
			1	45 (mean)	NS	RR	NFI			
			1	45 (mean)	NS	RR	NFI			
			1	45 (mean)	NS	SP	NFI			
			1	45 (mean)	NS	SP	NFI			
5	Voskresenskaya ¹⁶	2019	1	–	NS	PP	NFI			
6	Piotr Iwanowski ⁸	2019	1	24	F	PP	NFI			Genetic aspects
7	Magun et al. ¹⁷	2018	1	13	F	RR	NFI			
8	Gillani et al. ¹⁸	2017	1	25	F	SP	NFI			
9	El-Heis et al. ¹⁹	2017	1	33	M	NS	NFI			
			1	–	F	NS	NFI			
			1	40	F	NS	NFI			
			1	30	M	NS	NFI			
			1	30	F	NS	NFI			
10	Solaf Elsayed et al. ²⁰	2017	1	30	F	RR	NFI			
11	Mohebi et al. ²¹	2015	1	32	F	PP	NFI			
12	Madubata et al. ¹¹	2015	25	–	–	–	NFI			No clinical information
13	Jin et al. ²²	2014	1	65	F	RR	NFI			
14	Pipatpajong et al. ⁹	2011	1	28	M	PP	NFI			Genetic aspects
15	Spinicci et al. ²³	2010	1	17	F	RR	NFI		13 years	
16	Etamadifar et al. ²⁴	2009	1	19	F	PP	NFI			
			1	33	F	SP	NFI			
			1	36	F	SP	NFI			
			1	30	F	SP	NFI			
			1	26	F	RR	NFI			
			1	13	F	RR	NFI			
			1	16	M	RR	NFI			
17	Feuillet et al. ²⁵	2004	1	35	F	SP- > RR	NFI			
18	Perini et al. ²⁶	2001	1	19	M	RR	NFI		1 year	
			1	30	F	SP	NFI		14 years	
			1	45	M	PP	NFI			
19	Pàl et al. ²⁷	2001	1	37	F	P	NS			Glioblastoma
20	Johnson et al. ¹⁰	2000	0	–		PP*	NFI			Genetic aspects
			0	–		PP*	NFI			
			0	–		PP*	NFI			
			0	–		PP*	NFI			
			1	24	M	PP	NFI			
21	Masson et al. ²⁸	1997	1	–	NS	NS	NFI			
22	Alfonso et al. ²⁹	1996	1	–	NS	RR	NFI			
23	Ferner et al. ¹²	1995	1	44	F	PP	NFI		1 year	
			1	23	F	PP	NFI	Yes	19 years	
			1	32	F	PP	NFI		5 years	
			1	42	F	PP	NFI	Yes	20 years	
			1	65	M	PP	NFI		19 years	

(DMF) is hypothesized to provide clinical benefit to MS patients in case of ischemic stroke.³³

A small body of evidence suggests that the association between NF1 and MS might have a molecular explanation. The NF1 gene is located on chromosome 17q, contains 60 exons, and spans 350kb of genomic DNA. This gene is highly expressed in the myelin-forming oligodendrocytes which are the primary targets of the inflammatory and immune attacks in MS.³⁴

Conclusion

The association of NF1, MS, and CA can be considered as an expression of multiple factors: molecular explanation and the hiring of pharmacological treatments for MS that can increase the risk of stroke.

The onset of new neurologic symptoms and signs in patients with both NF-1 and MS should not always be considered an expression of the natural history of these two progressive diseases. Other overlapping acute pathologies should be kept in mind so as not to miss or postpone the correct diagnosis, and the consequent management (interventional, pharmacological, and rehabilitative treatment) should be appropriately applied.

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Author contributions

Laura Perucca (conceived and designed the article, revised it critically for important intellectual content), Francesca Morello (collected the data, performed the analysis, and wrote the paper), Antonio Robecchi Majnardi (conceived and designed the analysis, wrote the paper, and revised it).

Declaration of conflicting interests

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Ethics approval

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Informed consent

Written informed consent was obtained from the patient for their anonymized information to be published in this article; the patient could provide the written informed consent themselves.

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References

- Jouhilahti EM, Peltonen S, Heape AM, et al. The pathoetiology of neurofibromatosis 1. *Am J Pathol* 2011; 178: 1932–1939.
- Reich D, Lucchinetti CF and Calabresi PA. Multiple sclerosis. *N Engl J Med* 2018; 2(2): 169–180.
- Chandra A, Stone CR, Li WA, et al. The cerebral circulation and cerebrovascular disease II: Pathogenesis of cerebrovascular disease. *Brain* 2017; 3(2): 57–65.
- Terry AR, Jordan JT, Schwamm L, et al. Increased risk of cerebrovascular disease among patients with neurofibromatosis type 1: population-based approach. *Stroke* 2016; 47: 60–65.
- Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revision of the McDonald criteria. *The Lancet Neurol* 2018; 17: 162–73.
- Legius E, Messiaen L, Wolkenstein P, et al. Revised diagnostic criteria for neurofibromatosis type 1 and Legius syndrome: an international consensus recommendation. *Genet Med* 2021; 23(8): 1506–1513.
- Carvalho I, Quintas-Neves M, Pinto J, et al. Primary progressive multiple sclerosis in a Portuguese patient with neurofibromatosis type 1. *Cureus* 2021; 13: e20561.
- Iwanowski P, Kowalska M, Predecki M, et al. Primary progressive multiple sclerosis and neurofibromatosis type 1. *Mult Scler Relat Disord* 2019; 32: 66–69.
- Pipatpajong H and Phanthumchinda K. Neurofibromatosis type I associated multiple sclerosis. *J Med Assoc Thailand* 2011; 94(4): 505–10.
- Johnson MR, Ferner RE, Bobrow M, et al. Detailed analysis of the oligodendrocyte myelin glycoprotein gene in four patients with neurofibromatosis 1 and primary progressive multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2000; 68(5): 643–646.
- Madubata CC, Olsen MA, Stwalley DL, et al. Neurofibromatosis type 1 and chronic neurological conditions in the United States: an administrative claims analysis. *Genet Med* 2015; 17(1): 36–42.
- Ferner RE, Hughes RAC and Johnson MR. Neurofibromatosis 1 and multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1995; 58(5): 582–585.
- Ciotti S, Cometa A, De Carlo C, et al. Neurofibromatosis type 1 with highly active relapsing-remitting multiple sclerosis (RRMS). *Eur J Case Rep Intern Med* 2021; 8(3): 002190.
- Virgilio E, Vecchio D, Naldi P, et al. Efficacy of cannabinoids on spasticity and chronic pain in a patient with co-occurrence of multiple sclerosis and neurofibromatosis type 1. *Eur J Case Rep Intern Med* 2021; 8(5): 002424.
- Bergqvist C, Hemery F, Ferkal S, et al. Neurofibromatosis I and multiple sclerosis. *Orphanet J Rare Dis* 2020; 15(1): 2020.
- Voskresenskaya ON, Shmidt TE, Alekseeva AO, et al. Combination of multiple sclerosis and neurofibromatosis type I, remained undiagnosed from early childhood. *Voprosy Prakticheskoi Pediatrii* 2019; 14(3): 45–50.
- Magun R, Anand A, Mazhari A, et al. Full body Mri in neurofibromatosis type I. *The American Society of Neuroimaging* 2018; poster 42: 46.

18. Gillani R, Klawiter E and Jordan J. A large cervical spinal cord lesion in a patient with neurofibromatosis type 1: multiple sclerosis plaque or hamartoma. *Neurology* 2017; 88(16_supplement). https://doi.org/10.1212/WNL.8816_supplement.P3.161
19. El-Heis M, Gharaibeh M, Al-Omari M, et al. Multiple Sclerosis and Neurofibromatosis Type 1: report of seven patients from Iran. *Mult Scler* 2009; 15(9): 1126–1130.
20. Elsayed SM, Fahmy N, Gamal R, et al. Neurofibromatosis type 1 and multiple sclerosis: genetically related diseases. *Egypt J Med Human Genet* 2017; 18(3): 295–298.
21. Mohebi N, Moghaddasi M and Zaribafian M. Relapsing remitting multiple sclerosis in an Iranian patient with neurofibromatosis type I. *Neurol Int* 2015; 7(2): 25–27.
22. Jin Y, Segal D and Hillen M. An unusual case of neurofibromatosis type 1, high titer antinuclear autoantibodies and neuromyelitis optica. *Multiple Sclerosis* 2014; 354–355.
23. Spinicci G, Cherchi MV, Murru R, et al. A case of neurofibromatosis and multiple sclerosis. *Neurolog Sci* 2010; 31(5): 631–634.
24. Etemadifar M, Fatehi F, Sahraian MA, et al. Multiple sclerosis and neurofibromatosis type 1: report of seven patients from Iran. *Multiple Sclerosis* 2009; 15(9): 1126–1130.
25. Feuillet L, Boudinet H, Casseron W, et al. Multiple sclerosis associated with neurofibromatosis type I. *Rev Neurol (Paris)* 2004; 160(4 Pt 1): 447–451
26. Perini P and Gallo P. The range of multiple sclerosis associated with neurofibromatosis type 1. *J Neurol Neurosurg Psychiatry* 2001; 71(5): 679–681.
27. Pál E, Gömöri É and Gáti I. Neurofibromatosis and glioblastoma in a case of multiple sclerosis. *Eur J Neurol* 2001; 8(6): 717–718.
28. Masson C and Colombani JM. Neurofibromatosis I and multiple sclerosis. Apropos of a case. *Rev Neurol (Paris)* 1997; 153: 684–686.
29. Alfonso S, Roquer J and Pou A. Multiple sclerosis and neurofibromatosis 1. *Neurologia Barcelona* 1996; 233–235.
30. Robecchi Majnardi A, Malfitano C and Tesio L. COVID-19 pandemic: why time-dependent rehabilitation is forgotten. *Int J Rehabil Res* 2021; 44: 1–2.
31. Sabidó M, Venkatesh S, Hayward B, et al. Subcutaneous interferon- β 1a does not increase the risk of stroke in patients with multiple sclerosis: analysis of pooled clinical trials and post-marketing surveillance. *Adv Ther* 2018; 35(11): 2041–2053
32. Alnahdi MA, Aljarba SI and Al Malik YM. Alemtuzumab-induced simultaneous onset of autoimmune haemolytic anaemia, alveolar haemorrhage, nephropathy, and stroke: a case report. *Mult Scler Relat Disord* 2020; 41: 102141.
33. Owjifard M, Karimi F, Mallahzadeh A, et al. Mechanism of action and therapeutic potential of dimethyl fumarate in ischemic stroke. *J Neurosci Res* 2023; 101: 1433–1446.
34. Daston MM, Scrable H, Nordlund M, et al. The protein product of the neurofibromatosis type 1 gene is expressed at highest abundance in neurons, Schwann cells, and oligodendrocytes. *Neuron* 1992; 8(3): 415–428.