Neurofibromatosis I and multiple sclerosis

Christina Bergqvist, François Hemery, Salah Ferkal and Pierre Wolkenstein

Abstract

Neurofibromatosis 1 (NF1) is one of the most common autosomal dominant genetic disorders with a birth incidence as high as 1:2000. It is caused by mutations in the NF1 gene on chromosome 17 which encodes neurofibromin, a regulator of neuronal differentiation. While NF1 individuals are predisposed to develop benign and malignant nervous system tumors, various non-tumoral neurological conditions including multiple sclerosis (MS) have also been reported to occur more frequently in NF1. The number of epidemiologic studies on MS in NF1 individuals is very limited. The aim of this study was to determine the estimated population proportion of MS in NF1 patients followed in our Referral Centre for Neurofibromatosis using the Informatics for Integrated Biology and the Bedside (i2b2) platform to extract information from the hospital’s electronic health records. We found a total 1507 patients with confirmed NF1, aged 18 years (y) and above (mean age 39.2y, range 18-88y; 57% women). Five NF1 individuals were found to have MS, yielding an estimated population proportion of 3.3 per 1000 (0.0033, 95% Confidence Interval 0.0014–0.0077). The median age at diagnosis was 45 y (range 28–49 y). Three patients had relapsing-remitting MS and two patients had secondary progressive MS. Patients with NF1 were found to be twice more likely to develop MS than the general population in France (odds ratio 2.2), however this result was not statistically significant (95% Confidence Interval 0.91–5.29). Our results show that patients with NF1 might have a slight increased tendency to develop MS; however, due to the small sample size of our study, the results may not be sufficiently powered to detect this rare association. Large-scale epidemiological studies based on nationwide datasets are needed to confirm our findings. These findings further emphasize the need for a focused follow-up of patients with NF1, as early detection and management of MS can prevent further neurological disability.

Keywords: Neurofibromatosis 1, Multiple sclerosis, Autoimmune disease, Genodermatosis

Dear Editor,

Neurofibromatosis 1 (NF1) is one of the most common autosomal dominant genetic disorders with a birth incidence as high as 1:2000 [1, 2]. It is caused by mutations in the NF1 gene on chromosome 17 which encodes neurofibromin, a tumor suppressor protein [3, 4]. Neurofibromin regulates neuronal differentiation via its GTPase-activating protein function toward Ras [5]. By affecting multiple systems - including the cutaneous, neurologic, and orthopedic systems - NF1 leads to significant morbidity or mortality [2]. While NF1 individuals are predisposed to develop both benign and malignant nervous system tumors, various non-tumoral neurological conditions including learning disabilities [6] and attention deficit disorders [7] have also been reported to occur more frequently in NF1. Furthermore, NF1 has been linked to other chronic neurological conditions [8], such as epilepsy [9], sleep disorders [10], headaches [11], Parkinson’s disease [12], and multiple sclerosis [12].

Multiple sclerosis (MS) is the most common immune-mediated inflammatory demyelinating disease of the central nervous system (CNS) [13]. MS onset and course may depend on immunological, genetic and environmental factors [13]. Several case reports and small patient series have suggested an association between MS
Several case reports and case series have already indicated the potential association between NF1 and MS. [14–17] One large case-control study based on administrative claims data found a two-fold increased prevalence of MS in NF1 individuals; however, MS remains a rare complication of NF1 as it affects less than 1% of NF1 individuals (0.3% in our study).

A small body of evidence suggests that this association might have a molecular explanation. The NF1 gene is located on chromosome 17q, contains 60 exons and spans 350 kb of genomic DNA. This NF1 gene is highly expressed in the myelin-forming oligodendrocytes which are the primary targets of the inflammatory and immune attacks in MS [23]. NF1 gene inactivation in both mice [24] and zebrafish [25] results in increased oligodendrocyte precursor cells; and NF1 loss in genetically-engineered mouse models results in nitric oxide-mediated blood-brain barrier defects [26]. Furthermore, the gene for oligodendrocyte myelin glycoprotein OMG is embedded within intron 27b of the NF1 gene. OMG is a membrane glycoprotein that appears in the human central nervous system at the time of myelination [27]. This raises the possibility that impaired OMG function could affect myelinization, predisposing some NF1 individuals to MS. [18, 28] However, one study examined the OMG genes of four unrelated patients with NF1 and primary progressive MS and found that only two patients had alterations in the OMG gene. It was concluded that OMG mutations are neither necessary nor sufficient for primary progressive MS [18]. Moreover, one study found that a mutation in the OMG gene occurred in identical proportions in MS patients and healthy controls; making the OMG gene unlikely to be involved in the genetic susceptibility to MS [28].

Another suggested hypothesis relies in the role of the neurofibromin protein as a suppressor of cellular proliferation [29]. In NF1 patients, the absence of neurofibromin activity results in cell over-proliferation and tumor formation. Loss of NF1 in the Schwann cell lineage generates tumors composed of axonal processes, Schwann cells, fibroblasts, perineurial cells, and mast cells [30]. Hypothetically, if it also has a suppressor effect on the cells of the immune system, a loss of NF1 activity might result in over-activity of the immune system in some susceptible patients [31]. Furthermore, NF1 loss in NF1 genetically-engineered mouse models was also found to cause an altered myelin structure [26]. So, it might be possible that in patients with NF1, exposure of the immune system to an altered myelin peripherally might activate an autoimmune response to the myelin expressed in the CNS. Further mechanistic analyses are needed to elucidate the relationship between NF1 and MS pathogenesis.
Our study further confirms that the range of MS associated with NF1 includes different forms of the disease. Indeed, earlier reports on the association of NF1 and MS described patients with primary progressive forms of MS [15, 18]; but afterwards, other forms such as relapsing–remitting and secondary progressive MS associated with NF1 have been reported [14, 16]. Accordingly, three of our patients had relapsing-remitting MS and one patient had secondary progressive MS.

An important strength of our study is that all patients had a definitive diagnosis of NF1. An important limitation is the small sample size, which led to results not sufficiently powered to detect such a rare association. Another limitation is that it is a retrospective study based on the EHR of our Referral Center for Neurofibromatosis; this hospital-based recruitment may have led to a selection bias, as patients with MS and/or more severe forms of NF1 are more prone to seek medical care in a referral center and, therefore, may lead to an overestimation of the prevalence of MS. However, our findings are consistent with previous reports.

To conclude, our results show that patients with NF1 might have an increased tendency to develop MS. These findings further emphasize the need for a focused follow-up of patients with NF1. Early detection of MS in NF1 individuals is crucial as early management could prevent further neurological disability. Large-scale epidemiological studies based on nationwide data sets are needed to confirm our findings.

Abbreviations
NF1: Neurofibromatosis 1; MS: Multiple sclerosis; 12b2: Integrated Biology and the Bedside; CNS: Central nervous system; EHR: Electronic health records

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Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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