Editorial



# Are neurofibromatosis type 1 (NF1) patients at increased risk of meningioma and in particular malignant meningioma?

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In the current edition of the journal AlAnsari *et al.* report a case of a young woman with neurofibromatosis type 1 (NF1) who had developed an anaplastic meningioma (1). Around 1 in 67 people are diagnosed with a brain tumour in their lifetime (https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/brain-other-cns-and-intracranial-tumours/risk-factors). Meningiomas make up around 1/3 (2) of these inferring that around 1 in 200 people will be diagnosed with meningioma in their lifetime. This rises further to 1 in 110 people who have asymptomatic meningiomas on MRI at an average age of 63 years (3). There is a higher incidence in adult women, with only 1–3% falling into the malignant forms (4). As such between 1 in 6,700 and 1 in 20,000 people would be expected to develop a malignant meningioma. NF1 has a birth incidence of between 1 in 2,000 and 1 in 2,800 (5,6). Therefore, these are two rare diseases and a country the size of Italy (population 60 million) would only be expected to have one person alive today who would have NF1 and develop a malignant meningioma if the lower estimates of incidence were used. It is important that rare disease associations are reported such as this so that these can be explored further by subsequent reports or large NF1 or meningioma cohort studies. In reality even whole population studies in countries like Finland with over 1,400 NF1 patients identified (7) would not be large enough to validate any association unless the odds ratio was more than 10-fold population levels. The reporting of just two cases of an association in a small country like Finland would be sufficient to validate a likely association, but only one malignant meningioma was included in the Finnish series (7,8) (Peltonen J personal communication). A seminal review of central nervous system (CNS) tumours in the neurofibromatoses did not report any association between NF1 and meningioma let alone malignant meningioma (9). Indeed, cohort studies should be able to easily assess any link with meningioma as a whole. One cohort study from the UK reported only one meningioma in 523 NF1 patients (10). A total of seven meningiomas have been diagnosed in the Finnish cohort of 1,482 individuals (0.47%–Peltonen J personal communication) with NF1 (7,8). An update from our UK study has only found 8 NF1 patients with a single meningioma (0.27%) out of 2,909 total equivalent to 1 in 363 individuals. Given that about 30% of our NF1 patients have received a brain MRI this does not seem likely to represent an increased risk. Using the search term 'meningioma risk and NF1' in PubMed only two other cohort study have been reported with 1/69 NF1 patients having a single meningioma in a Taiwanese series (11). The contentious series was reported from the USA where a 65-year history of paediatric meningiomas was reported from a single institution (12). The authors reported that

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eight of 39 patients had neurofibromatosis with 4 being classified as NF1. However, on closer inspection the diagnosis of NF1 is highly debatable in the four cases. Firstly, these cases dated between 1963 and 1975 well before the formal separation of NF1 and NF2 by the National Institutes of Health consensus conference in the USA in 1986. Before that time many series included individuals with bilateral acoustic neuromas (vestibular schwannomas) as having von Recklinghausen neurofibromatosis the classical descriptor for NF1. This is exemplified by the series from Frank Crowe from 1956 (13), in which 5% of patients had bilateral 8$^{th}$ cranial nerve tumours. Secondly the description in the case series (12) of associated tumours is much more in keeping with NF2 with the exception of optic glioma "Three patients—and an unconfirmed fourth case—had NF1 one of whom also had multiple intracranial meningiomas. In these patients, optic gliomas, cervical neurofibroma, cerebellopontine angle schwannoma, cauda equina schwannoma, schwannoma of appendix and pericardium, and neurofibromas of the oculomotor nerves were also observed". Although neurofibromas are a feature of NF1 not NF2 the pathologies are often intermingled (14,15) and the presence of multiple meningiomas and cerebello-pontine angle schwannoma (most likely vestibular schwannoma) in a child with meningioma would be vastly more likely to be NF2 than NF1. Indeed, the paper does not make a good case for any definite confirmed case of NF1. In the absence of a clear association between meningiomas as a whole it seems unlikely that NF1 will be associated with malignant meningioma, but only by combining large series of NF1 patients will any lack of association be confirmed.

A salient point when searching for associations between rare conditions and rare tumour types is to make sure of the source of any reported association (16). In a report of 173 cases of childhood medulloblastoma we reported a single case of NF1 (16). However, the literature reported an increased risk of medulloblastoma in NF1 that all related to a single case (17). This would clearly not have been sufficient to verify an association even with a second report. Since then, a recent paper reported a medulloblastoma-NF1 association including 9 further cases from the literature (18), although they missed the association reported by ourselves (16). Nonetheless, given that there are now 11 reported cases of NF1 and paediatric medulloblastoma with a childhood risk of around 1 in 10,000 for medulloblastoma in childhood (19) a link between NF1 and childhood medulloblastoma seems more likely than with malignant meningioma at any age given that there has thus far been only one report albeit that a further case was identified in the Finnish series (1,7).

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