Vestibular Schwannoma in a patient with Neurofibromatosis Type 1: Clinical Report and Literature Review

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ABSTRACT

We describe a young patient with typical Neurofibromatosis Type 1 on the basis of a mutation in the *NF1* gene, who was diagnosed with a unilateral Vestibular Schwannoma caused by a somatic mutation in the *NF2* gene. This combination has not been described before. This report highlights the requirement for ongoing surveillance regarding other manifestations of Neurofibromatosis Type 2 in such patients, as mosaicism cannot be ruled out. In addition to the *NF1* mutation, the *NF2* mutation should be considered in such cases if pre-implantation genetic diagnosis in undertaken.

Key words: Neurofibromatosis, Vestibular Schwannoma, NF1 and NF2

INTRODUCTION:

Neurofibromatosis type 1 (NF1) (OMIM162200) is an autosomal dominant genetic disorder characterised by multiple café au lait macules, intertriginous freckling, neurofibromas, iris hamartomas and osseous lesions [1]. Neurofibromatosis type 2 (NF2) (OMIM 101000) is another autosomal dominant condition which results in vestibular schwannomas, intracranial meningiomas, spinal tumours and peripheral nervous system tumours, in addition to posterior subcapsular lens opacities [2].

Whilst NF1 and NF2 share a descriptor, they are clinically and genetically distinct identities. The *NF1* gene is located on chromosome 17q11.2 [3] and the *NF2* gene on chromosome 22q12.2 [4, 5]. Co-existent findings of both NF1 and NF2 have been few, other than occasional café au lait macules and neurofibroma of the skin. Malignant schwannoma has been described in NF1 [6, 7], but to the best of our knowledge, vestibular schwannoma or acoustic neuroma, the hallmark of NF2, is not a syndromic feature of NF1. In this case report, we describe the occurrence of a somatic mutation in the *NF2* gene causing a unilateral vestibular schwannoma in a 27 year old man with a germline mutation in the *NF1* gene.

CLINICAL REPORT:

The proband was diagnosed with NF1 at the age of 11 when he underwent surgical removal of a non-erupted tooth due to an overlying maxillary neurofibroma. He is the eldest of two children born to non-consanguineous parents of Italian origin. In addition to the left maxillary neurofibroma, he had multiple café au lait spots, axillary freckling, and neurofibromas on chest wall, as well as mild thoracolumbar scoliosis. Subsequent to his diagnosis, his mother was also diagnosed with NF1 due to the presence of multiple neurofibromas and café au lait macules.

Based on his clinical signs, the proband fulfils the National Institutes of Health (NIH) diagnostic criteria for NF1. He has required recurrent surgical excision of the left maxillary neurofibroma as a child which has resulted in facial asymmetry. He had learning difficulties particularly with mathematics and had behavioural issues as a child. An ophthalmological examination in his early 20s revealed Lisch nodules with no evidence of posterior subcapsular lenticular opacities. The proband has been an active sportsman and has maintained fulltime employment since

completing secondary school. He has been reviewed on an annual basis and has not had any other complications from NF1.

Apart from requiring surgical excision of some neurofibromas due to pain and discomfort, the proband's mother has not had any NF1 related complications. The proband's brother does not have any clinical features of NF1, nor does any other member of their large family.

At the age of 27, the proband reported a six month history of tinnitus, headaches and vertigo. Audiometry revealed mild to moderate left sided sensorineural hearing loss. An MRI scan of his brain identified a large left sided tumour consistent with a vestibular schwannoma, measuring 4.5cm with significant brainstem and cerebellar compression, filling the internal auditory canal. An enhancing lesion in the left pre-vertebral region was also found, the nature of which was not clear. The size of the cerebellar tumour and the symptoms warranted surgical removal. Histological examination confirmed this to be a vestibular schwannoma. He is yet to have a spinal MRI and hence we are unable to exclude any spinal lesions. The proband required in-patient rehabilitation due to difficulties with balance and mobility, which have largely resolved. However, he has been left with a moderate cranial nerve VII palsy.

The proband and his long-term partner sought information quantifying the risk of NF1 and NF2 in their future offspring and their reproductive options to reduce this risk. With informed written consent, mutation detection of the *NF1* and *NF2* genes were undertaken in DNA from his peripheral leukocytes. The vestibular schwannoma was tested for mutations in the *NF2* gene.

Genetic Test Results:

NF1: A heterozygous variant in the *NF1* gene c.2975T>G was detected in the proband. This variant is predicted to result in a missense change at the protein level (p.Met992Arg). This variant has been reported once previously where it is described as being a de novo change in a patient with NF1 [8]. The testing laboratory had not observed this variant before and in silico analyses were inconclusive with regards to the pathogenicity. The proband's affected mother has subsequently been found to harbour the same mutation. More spreading is required, along with functional studies before this mutation could be reclassified as pathogenic.

NF2: Testing was undertaken on the vestibular schwannoma and the proband's genomic DNA for mutation(s) in the *NF2* gene. A sequence variant c.1575delA in exon 15 of the *NF2* gene was identified in the vestibular schwannoma tumour sample. Loss of heterozygosity analysis was performed at three polymorphic markers D22S929 located in intron 1, intragenic locus NF2CAV and locus D22S275 located 1cM distal to the NF2 gene. Loss of heterozygosity was detected in all three loci for the tumour sample. This sequence variant was not found in the blood DNA sample. No other variants in the *NF2* gene were detected in the blood DNA sample.

The c.1575delA mutation has been listed once in the Catalogue of Somatic Mutations in Cancer (COSMIC) database in association with disease. It has not been listed in the Human Genetic Mutation Database (HGMD) professional 2014.1 (Biobase). It is predicted to affect acceptor site splicing (http://www.cbs.dtu.dk/services/NetGene2/) and the C-terminal (codons 479-595) protein domain. Studies have shown that for the NF2 protein, merlin, to function as a tumour suppressor there needs to be self-association between the N-terminal and C-terminal domains of the protein [9]. This variant has previously been reported in a patient with sporadic schwannoma [10]. The effect of this mutation on the acceptor splicing remains uncertain in the absence of RNA studies. However, it is likely to severely disrupt the functionality of merlin protein and consequently predicted to be pathogenic in nature.

DISCUSSION:

To our knowledge, this combination of NF1 and unilateral vestibular schwannoma has not been previously described. The evolution of the understanding of these two separate conditions has led to their clinical divergence, despite NF1 and NF2 historically being considered "awkward bedfellows" [11].

NF1 is an autosomal dominant condition caused by germline inactivating mutation in the *NF1* gene on chromosome 17, affecting all geographic and ethnic groups equally [12]. Mutations in the *NF1* gene affect the Ras/MAPK pathway [3]. Loss of the *NF1* gene product neurofibromin causes hyperactive Ras signalling [13]. About 50% of cases of NF1 are inherited with the other 50% being due to de novo *NF1* mutations. The condition is fully penetrant but shows considerable variability in expression. Modifier genes are thought to cause this variability [14].

Spits et al in 2005 reported the exact *NF1* variant as described in this case report, in one of the participants in their study. A male with clinical features of NF1 with the c.2975T>G mutation utilised pre-implantation genetic testing and the couple went on to have a successful pregnancy [8].

NF2 is generally characterised by the presence of bilateral vestibular schwannomas. Unilateral vestibular schwannoma before the age of 30 along with NF2 in a first degree relative is also considered diagnostic of NF2. The combination of unilateral vestibular schwannoma and an NF2 related tumour such as meningioma, glioma or schwannoma or the presence of posterior subcapsular lenticular opacity or cataract is another diagnostic criteria [2].

Vestibular schwannomas account for 8 to 9% of intracranial tumours and 80% of tumours found within the cerebellopontine angle. Bilateral vestibular schwannomas are uncommon and typically associated with NF2 [15]. Most unilateral vestibular schwannomas, after the age of 30, are likely to be sporadic and usually not associated with germline NF2 mutations [2]. However, there is evidence to suggest that patients who develop unilateral vestibular schwannoma under the age of 30 may have mosaic NF2. These patients are therefore at increased risk of developing bilateral vestibular schwannomas [16]. Evans et al state in their UK based population data analysis that the risk of NF2 in people presenting with unilateral sporadic vestibular schwannoma is 5.7% [17]. Absence of an *NF2* mutation in peripheral lymphocytes in these individuals cannot be used as a means of excluding NF2, because of the possibility of low level mosaicism below the detection level or mosaicism confined to tissues other than peripheral lymphocytes. In *de novo* cases of unilateral vestibular schwannoma, testing should begin in the tumour tissue as lack of a mutation in peripheral blood sample alone cannot be used to exclude NF2, particularly mosaicism [17].

Identification of the mutation in the tumour flags these patients as requiring ongoing surveillance for recurrence and also provides the opportunity to test offspring with regards to their necessity for surveillance [16].

Aghi et al in their retrospective study of 44 patients with unilateral vestibular schwannoma and other NF2 related tumours, but without a heterozygous *NF2* germline mutation identified the risk of contralateral vestibular schwannoma as being ~29% [18]. These individuals have a risk of bilateral

deafness, emphasising the importance of ongoing surveillance. It should however be noted that not all of these tumours were assessed for somatic mutations.

Evans et al reported in their study of 142 individuals with unilateral vestibular schwannomas that if a fully penetrant mutation is found in tumour alone and not identified in a peripheral blood sample, the risk of transmission to the offspring is around 1 in 12 [19]. If only point mutations in the tumour are considered, then Evans et al report the risk to offspring as being <5% [19].The risk to offspring if a unilateral VS is present in addition to another NF2 related tumour was calculated to be 20% in those developing the unilateral VS between 19 and 29 years of age [20]. In addition, the possibility of classic NF2 in the offspring of an individual with *de novo* mosaic NF2 must be considered when counselling these individuals.

There are some notable differences between the phenotypes of NF1 and NF2. It is unusual for individuals with NF2 to have Lisch nodules or significant numbers of café au lait macules. Likewise, the intellectual disability associated with NF1 is not a feature of NF2.

CONCLUSION:

This case demonstrates the unique and interesting combination of NF1 and unilateral vestibular schwannoma in the same person. The importance of *NF2* mutation testing in individuals presenting with unilateral vestibular schwannomas at a young age, even in the absence of a family history, is highlighted. It is important to discuss mutation testing and its application to family planning in this group of young individuals. There are currently no clear guidelines with regards to the risk for a second VS or transmission of NF2 to offspring in such cases.

The proband will have ongoing surveillance in the form of yearly MRI brain scans as his risk of contralateral vestibular schwannoma is increased, as well as surveillance for his NF1. Pregnancy options such as pre-natal diagnosis and pre-implantation genetic diagnosis can be discussed for both NF1 and NF2 in this family.

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