CLINICAL REPORT

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Vestibular Schwannomas Occur in Schwannomatosis and Should not be Considered an Exclusion Criterion for Clinical Diagnosis

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Schwannomatosis is a recently delineated inherited condition that has clinical overlap with neurofibromatosis type 2 (NF2). Diagnostic criteria have been developed to distinguish schwannomatosis from NF2, but the existence of mosaic NF2, which may closely mimic schwannomatosis, makes even these criteria problematic. In particular, it is not clear why there is a relative sparing of the cranial nerves from schwannomas in schwannomatosis. We have identified two individuals with schwannomatosis and a unilateral vestibular schwannoma (VS), where a diagnosis of NF2 has been excluded. A third case with an identified *SMARCB1* mutation was reported by two radiologists to have a VS, but this was later confirmed as a jugular schwannoma. These cases question whether the current exclusion of a VS from the clinical diagnosis of schwannomatosis is justified.

Key words: vestibular schwannoma; schwannomatosis; NF2; diagnostic criteria

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INTRODUCTION

The tumor suppressor syndromes schwannomatosis and neurofibromatosis type 2 (NF2) both predispose individuals to schwannomas. Despite their phenotypic similarities, schwannomatosis has been shown to be a distinct entity from NF2 [MacCollin et al., 2003], mainly due to the absence of a vestibular schwannoma (VS). Recently a proportion of schwannomatosis families and a minority of sporadic schwannomatosis patients were shown to be due to mutations in the *SMARCB1* gene, which is centromeric to the *NF2* gene on chromosome 22q [Hulsebos et al., 2007; Boyd et al., 2008; Hadfield et al., 2008; Sestini et al., 2008].

Almost all non-mosaic NF2 patients develop bilateral VS [Evans et al., 1992], while current diagnostic criteria for schwannomatosis specifically exclude the presence of schwannomas on vestibular nerves [MacCollin et al., 2005]. However, mosaic NF2 patients, affected in only one portion of the body, may never develop VS and may be confused with schwannomatosis if no *NF2* mutation is identified.

It is currently unclear why the cranial nerves are left relatively unaffected by schwannomas in schwannomatosis. Here, we report on two individuals with a positive clinical diagnosis of schwannomatosis who have also developed a unilateral VS. A third case with definite schwannomatosis and a germline *SMARCB1* mutation was initially thought to have a VS. This questions the current thinking that VS do not occur in schwannomatosis.

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CLINICAL REPORTS

Patient 1

A 53-year-old man was seen with a history of subcutaneous and spinal schwannomas and a unilateral VS. He presented at the age of 24 with shooting pains in his right arm. A subcutaneous tumor affecting his right upper arm was surgically removed and confirmed on histology to be a schwannoma. At around age 32, he developed shooting pains in his right leg. Subsequent investigations at Dusseldorf University clinic identified a spinal "neurofibroma". This was removed at the National Hospital for Neurology and Neurosurgery, London, the same year. Five years later, he developed tinnitus in his right ear and a right VS was diagnosed by imaging. This tumor was subsequently removed at the Stadt-Krankenhaus, Hanover. This was a successful operation with no hearing impairment, although he was left with a degree of persistent tinnitus. At age 43, he developed back pain due to nerve entrapment. Magnetic resonance imaging (MRI) showed a new spinal schwannoma in his right conus region, which was removed at the National Hospital for Neurology and Neurosurgery in 2001.

He was promptly referred to the genetics clinic for genetic counseling in view of his history and the putative diagnosis of NF2 in his family. Notably, his father had had a spinal "neurofibroma" removed at the National Hospital for Neurology and Neurosurgery at the age of 55, although the pathology report clearly states "schwannoma". He was left with lower limb weakness but did not have any spinal tumor recurrences. He also had a history of subcutaneous lumps being removed from the face at 21 and 24 years of age, and from the upper right arm at 49 years of age. Surgery for a subcutaneous lump in the left wrist at age 63 identified another schwannoma. VS has not been diagnosed in this man at the age of 80. He is able to talk on the telephone and recently had whole body MRI after a diagnosis of melanoma, and there were no cranial tumors. The index patient's paternal uncle and his two brothers also had subcutaneous and spinal schwannomas, but none of these family members had developed a VS at the ages of 76, 47, and 48. One son of the affected uncle was found to have two thoracic schwannomas at age 51, again with no VS or other intracranial tumor. Our patient's main concern at the time was regarding the risk to his daughter and son, aged 5 years and 14 months, respectively. On examination, the children did not have clinical signs of the condition. Furthermore, his daughter had had a recent audiometry test, which was reported to be normal. Ophthalmological assessment of the children and their father was arranged. No lens opacities or fundus abnormalities were noted in either the father or the children.

It was proposed that the family may have a diagnosis of schwannomatosis rather than NF2. Previous linkage analysis using intragenic and flanking markers showed tight linkage to the *NF2* gene [Evans et al., 1997]. However, full mutation analysis with sequencing and multiple ligation dependent probe amplification (MLPA) did not identify any mutations. The *SMARCB1* gene has also been fully sequenced and undergone dosage analysis by MLPA, but no abnormalities were found. To confirm this result, fresh blood samples were obtained from the patient for further mutation analysis. Confirmatory tumor tissue analysis could not be performed.

Notably, the patient had no previous screening for his condition. In line with guidance at the time, it was felt that he should have regular surveillance for the development of recurrences or new vestibular and spinal schwannomas. He was therefore referred to the National Hospital for Neurology and Neurosurgery for annual neurological review and craniospinal imaging every 3 years. Subsequent MRI of his brain and spine showed no evidence of residual or recurrent VS but showed three new spinal lesions; the first lesion was a rounded extra-medullary enhancing mass on the left, posterolateral to the cord at C4/5; a second small lesion posterior at the conus and possibly related to the cauda equina at the level of L2; and, a third slightly larger lesion related to the right L5 nerve root. The appearances were in keeping with multiple schwannommas although at the time our patient was free of symptoms other than the known unchanged tinnitus in his right ear. He was therefore kept under annual review by the neurosurgeons with no immediate plans for surgical intervention.

He was reviewed in the genetics clinic in 2005, together with his two children, aged 10 and 6 years. He remained clinically well, his only new symptom of note being intermittent shooting pains in his right hand. On examination, he had a firm 1×2 cm subcutaneous mass in the right posterior triangle of his neck.

In 2006, repeat imaging demonstrated a tiny enhancing nodule within the right internal acoustic meatus, thought to be recurrence of his right VS. Furthermore, the spinal lesion at C4/5 had increased in size and there was a T8/9 lesion not seen on the previous study. The spinal schwannoma at C4/5 was removed in 2007 and subsequent spinal imaging in 2008 has shown no further change in the multiple schwannomas affecting our patient's spine.

Patient 2

A 55-year-old man first presented to the genetics clinic with a long history of painful subcutaneous tumors in his right forearm. He first noticed the lumps aged 17 and the first schwannoma was removed from the right ulnar nerve at age of 18. The second schwannoma was removed from the left middle finger at age 23. There then followed a period of quiescence until the age of 53 when pain recurred around the right wrist and hand. MRI scan showed several schwannomas from the left elbow to wrist on the line of the ulnar nerve. Four further schwannomas were removed at this time from the ulnar nerve and one from the median nerve. Clinical examination at age 55 showed evidence of bilateral schwannomas along the ulnar nerves but no other obvious cutaneous or subcutaneous tumors. Ophthalmic examination showed no evidence of lens opacities on slit lamp examination. An NF2 cranial MRI protocol was performed with 3 mm cuts through the internal auditory meatuses with gadolinium enhancement. A small left-sided intracanalicular VS measuring about 10 mm in diameter was identified as well as a small presumed schwannoma at T5 on spinal imaging. Five years later this had grown to 17 mm and was already causing hearing loss. The tumor was removed through a trans-labyrinthine approach and noted to arise on the inferior vestibular nerve. Histology confirmed it to be a benign VS. Follow-up imaging at age 62 showed no evidence of tumor recurrence, no right-sided VS and no other intracranial tumors. The T5 spinal lesion had not grown in 8 years.

The patient had no family history of nerve related tumors. Initial *NF2* mutation analysis by direct sequencing on blood lymphocyte DNA failed to identify a mutation. DNA from one of his peripheral nerve schwannomas was examined for all 17 *NF2* exons by single strand conformation polymorphism analysis. Microsatellite analysis of the intragenic marker, *NF2CA3,* and flanking marker, *NF2S275*, showed no evidence of loss of heterozygosity (LOH). Subsequently fresh tumor from the VS became available and analysis of DNA extracted from this tumor identified a c.241-2A > C splicing mutation in exon 3. This mutation was not present in lymphocyte DNA or his previous schwannoma. Microsatellite analysis showed significant LOH at both markers, but dosage analysis with MLPA showed no deletions in *NF2*. These results are consistent with either mitotic recombination (MR) or loss of the normal chromosome 22 with reduplication of the chromosome carrying the *NF2* mutation. Microarray analysis confirmed that this was due to MR [Hadfield et al., 2010]. *SMARCB1* mutation analysis failed to identify a mutation.

Family 3

A male with a known family history of neurogenic tumors underwent surgery for an intraspinal tumor at age 65. Histology determined the tumor to be a schwannoma. Cerebral MRI at the same age was reported to show a unilateral right-sided VS measuring 13.5 × 14.5 × 16.5 mm in the cerebello-pontine angle (see Fig. 1). He had previously undergone surgery for excision of a schwannoma under the right coracoid process at age 43. In addition, at age 65, he had multiple intraspinal lesions as well as right and left cauda equina lesions. He has significant pain in his left leg, but surgery has not been advised thus far. His hearing was slightly reduced on the right side. A second cranial MRI scan was also reported to show a VS, but this had not grown.

His daughter, was given a presumptive diagnosis of NF2 when she was first seen in the genetics clinic in 2005, at age 26. At initial presentation, aged 15, she had a 3-year history of progressive fatigue, impaired balance, increasing headaches and emesis. Cranial CT and subsequent MRI showed a large tumor in the right cerebello-pontine angle and marked supratentorial hydrocephalus. The tumor, which was partially excised, arose from the trigeminal nerve. Histopathologically it was judged to be a schwannoma. Six further schwannomas were identified in the following 13 years including a further intracranial tumor close to the right optic nerve. Her last cerebral MRI in 2007 (aged 28) showed no evidence of a VS, nor has she developed symptoms suggestive of such a lesion.

Family history identified a sister who had two schwannomas removed at age 26, one from her neck and one from her wrist. Furthermore, her sister underwent surgery for a brain tumor at age 27. The pathologist concluded that histology was compatible with a malignant tumor of neurogenic origin. She died at age 30 of complications related to the brain tumor. Her other sibling, a 32-year-old brother, was healthy. The paternal grandmother had a tumor, which was histologically reported to be a neurinoma, removed from her throat at age 31, in 1950. She developed a brain tumor, which was resected 6 years later. It has not been possible to retrieve the histological report, but the national cancer registry noted that the lesion was a ganglionic neurinoma. She died at age 42.

After the daughter visited the clinic in 2005 her father and brother were offered surveillance based on the diagnosis of NF2. A blood sample from the daughter was sent for *NF2* gene testing, but no mutation or LOH was detected. She was re-referred to the clinic at age 31, as she was concerned that her 5-year-old son could develop NF2. At this visit, schwannomatosis was suspected and analysis of the *SMARCB1* gene was requested. Sequence analysis in a blood specimen identified a truncating mutation, c.34C > T (p.Gln12X) in exon 1 of *SMARCB1*, confirming the clinical suspicion of schwannomatosis. The mutation was detected in blood from the father, but not in the healthy brother.

Recent review of the right cerebello-pontine angle tumor, after discovery of the *SMARCB1* mutation in the father by the authors,

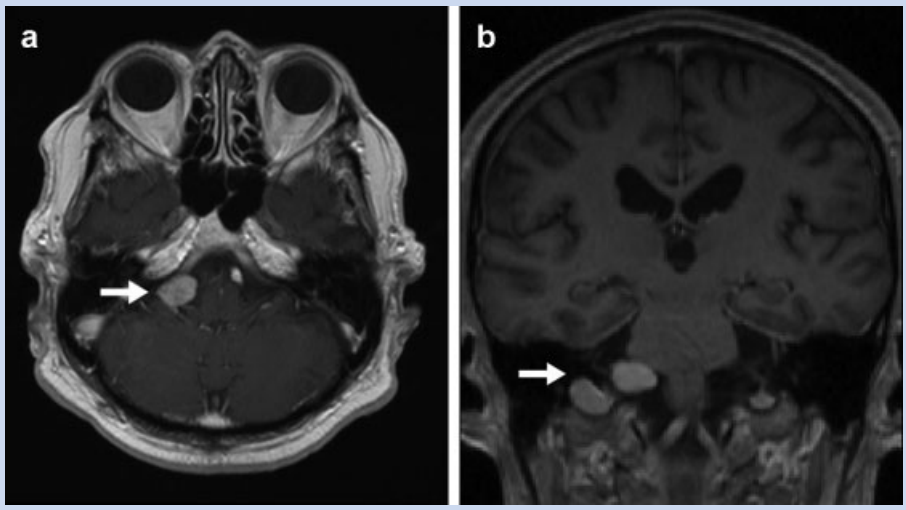

FIG. 1. a,b: Axial and coronal views of the right cerebello-pontine angle schwannoma in Patient 3.

has shown that this is more likely to be a jugular schwannoma with extension of the tumor down the jugular foramen but not into the internal auditory meatus.

In view of the concern over the potential mis-diagnosis of NF2 in schwannomatosis cases with *SMARCB1* mutations, we reviewed 34 patients with *SMARCB1* mutation positive schwannomatosis in the Manchester schwannomatosis database. Eight of these (23%) had evidence of an intracranial tumor consistent with a schwannoma, including all four members of Family 3. Five of these tumors arose in the cerebello-pontine angle.

DISCUSSION

We describe three individuals with schwannomatosis whose diagnoses were untenable due to the presence, or reported presence, of a unilateral VS [MacCollin et al., 2005]. All three patients would have been technically diagnosed as having NF2 due to the presence of a unilateral VS and two or more additional schwannomas [Baser et al., 2002]. However, for Patient 1 the absence of VS in five other affected family members makes NF2 very unlikely and for Patient 2 an *NF2* mutation has been excluded as the cause of his schwannoma predisposition. For Patient 3, the presence of a pathogenic *SMARCB1* mutation confirms definite schwannomatosis. Mutation sensitivity in the second generation of NF2 families is 92% [MacCollin et al., 2003], therefore in the families of Patients 1 and 3 a missed *NF2* mutation would be very unlikely. Patients 1 and 2, each with a definite VS, show a pattern of subcutaneous painful peripheral nerve and spinal tumors typical of schwannomatosis. Tumors from Patient 2 also show somatic inactivation of *NF2* with different *NF2* mutations in each schwannoma [MacCollin et al., 2003]. The presence of identical *NF2* mutations would have confirmed mosaic NF2 [Murray et al., 2006]. It is of course possible that all three patients had a "sporadic" VS and this was not caused by the underlying schwannomatosis disease. Nonetheless, it seems likely that, even with *SMARCB1* mutations, there will be some excess of VS above the 1 in 1,000 risk seen in the general population [Evans et al., 2005]. In view of the long delay in a correct diagnosis in Family 3 caused by the cerebello-pontine angle tumor being reported as VS, we have reviewed the presence of intracranial schwannoma and found that 24% of 34 *SMARCB1* mutation-positive schwannomatosis patients had evidence suggestive of vestibular schwannoma. Five of these tumors occurred in the cerebello-pontine angle and many non-expert radiologists would presume these were vestibular schwannomas. One of these was a tumor removed in the 1980s from the IX cranial nerve, which presented as a large cerebello-pontine angle tumor on CT scan and was, at that time, indistinguishable from a VS. The four others were trigeminal schwannomas that appeared in the cerebello-pontine angle with a further trigeminal in the cavernous sinus. While we are now confident that Patient 3 does not have a VS, his case illustrates that VS may be misdiagnosed in schwannomatosis and therefore throw uncertainty on the diagnosis. While it is sensible to exclude VS in research criteria for schwannomatosis, it is likely that this exclusion has deterred clinicians from investigating whether patients with a unilateral VS and other schwannomas may have schwannomatosis. Indeed, the literature is likely to be biased against including VS amongst schwannomatosis cases. We currently have these two confirmed cases with unilateral VS amongst 178 schwannomatosis patients on our Manchester Schwannomatosis database. This is higher than would be consistent with the chance of VS seen in the general population. In addition, a further family containing three siblings with multiple schwannomas and unilateral VS has not been shown to be due to germline mutation of either the *NF2* or the *SMARCB1* gene. For the purpose of investigation of the underlying cause of schwannoma development a unilateral VS should lead to tumor analysis of the *NF2* gene if possible and any identified *NF2* mutation should be confirmed in a second tumor or in lymphocyte DNA. Unless an identical *NF2* mutation is found in more than one tumor or in blood DNA then a diagnosis of NF2 cannot be certain. If the family pattern is more consistent with schwannomatosis as for Patient 1, or if a second tumor does not carry an identical mutation, then schwannomatosis is the more likely diagnosis. Although we have shown that VS can occur in cases of schwannomatosis, further work is necessary to determine the risk of VS in both *SMARCB1* mutation-positive and *SMARCB1* mutation-negative schwannomatosis.

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