

Spinal Schwannomatosis without NF Syndrome: State of the Art

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ABSTRACT

Schwannomas are encapsulated and slow growing benign peripheral nerve tumors. They represent about one third of all benign primary spinal tumors. Most schwannomas occur as isolated lesions, but it could be possible to find a multiple localization involving one or more nerves. The presence of multiple schwannomas in a single patient is suggestive of a genetic predisposition to tumorigenesis and a possible association with syndromes such as neurofibromatosis (NF). Schwannomatosis is defined as an extremely rare tumors syndrome characterized by the presence of multiple schwannomas in the absence of typical signs of NF1 and NF2 syndromes. The genetic and molecular analysis of the tumors, revealed, therefore, that it is possible to frame schwannomatosis as distinct clinical and genetic syndrome. Usually, patients with schwannomatosis develop cranial, spinal or peripheral nerve schwannomas but do not develop vestibular lesions (VS), typical of NF2. Moreover, even the genetic features are different respect to neurofibromatosis, allowing to classify the disease as a distinct nosological entity. The treatment, up to us, in case of symptomatic lesions is surgical removal; in case of asymptomatic lesions is important, instead, to perform serial MRI studies. Moreover, even the genetic features are different respect to neurofibromatosis, allowing to classify the disease as a distinct nosological entity. Furthermore given the high incidence of developing additional lesions in patients with Schwannomatosis, it remains imperative to perform serial brain and spinal cord MRI studies during follow-up time. Important is the differential diagnosis including clinical and radiological criteria plus molecular genetic analysis of tumor cells and lymphocyte DNA. The aim of this editorial is to analyze the state of the art about diagnosis,

treatment and follow-up about this extremely rare pathology, often misdiagnosed or confused with other pathologies such as NF syndromes, highlighting the extremely high relevance of molecular genetic study to correctly identify it.

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Key words: Spinal schwannomatosis; Neurofibromatosis; Surgery; Multiple schwannomas; NF syndrome; NF1; NF2

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INTRODUCTION

Schwannomatosis is defined as an extremely rare tumors syndrome characterized by the presence of multiple schwannomas in the absence of typical signs of NF1 and NF2 syndromes. Schwannomas are encapsulated and slow growing benign peripheral nerve tumors. They represent about one third of all benign primary spinal tumors. Most schwannomas occur as isolated lesions, but it could be possible to find a multiple localization of schwannomas involving one or more nerves. The presence of multiple schwannomas in a single patient is suggestive of a genetic predisposition to tumorigenesis and a possible association with syndromes such as neurofibromatosis (NF).

NEUROFIBROMATOSIS

Neurofibromatoses are a heterogeneous group of genetic disorders predisposing to various tumors of the nervous system. Among the different variants of NF only for type 1 neurofibromatosis (NF1) and type 2 neurofibromatosis (NF2)^[1], National Institute of Health (NIH) have established the guidelines for the diagnosis as described in the literature. NF1 is the most common form, with an incidence at birth of 1 / 2500. NF1 is a common autosomal dominant neurocutaneous disorder characterized by multiple café au lait spots, axillary and inguinal freckling, multiple cutaneous neurofibromas, and iris Lisch nodules^[2]. NF-1 is caused by loss of function mutations in the NF1 gene in 17q11.1. This leads to defective production of neurofibromin, a guanosine triphosphatase-activating protein that

helps maintain the protooncogene Ras in its inactive form^[3]. Loss of neurofibromin predisposes to increased tumorigenesis, and malignant disease can appear in either childhood or adulthood, with malignant peripheral nerve sheath tumours (MPNSTs) being most common^[4]. Several pathways are thought to be involved in the development of tumours associated with NF1: rat sarcoma viral oncogene homologue (RAS)-mitogen-activated protein kinase (MAPK), mammalian target of rapamycin (mTOR), and P21 protein (Cdc42/Rac)-activated kinase 1 (PAK1)^[5,6]. NF-1 patients have a lifetime risk of 8-13% to develop MPNSTs, which are the leading cause of NF1-related mortality. In current clinical practice the diagnosis of MPNST should always be considered in NF-1 patients, especially those with persistent pain (that lasts over 1 month or disturbs sleep), new neurological deficits, or alteration in the characteristics of a known neurofibroma^[7]. Surgical resection is the mainstay of treatment; however, because of increased metastatic potential and resistance to chemotherapy and radiation the prognosis is poor. Five-year survival rates still only reach 20-50%, despite latest efforts to identify potential molecular targets^[8]. MPNSTs should be included in the differential diagnosis of persistent or atypical pain in a young adult. Although rare, these malignancies are commonly associated with NF-1 and can be the first manifestation of the disease, as this case illustrates. Early diagnosis is paramount as survival rates are extremely poor in advanced stages of the malignancy.

The NF2, much less common than the previous one (incidence at birth of approximately 1 / 33000), is associated with significant morbidity and mortality due to the frequent localization of the lesions in the brain and in the spinal cord. The mutation in the NF2 gene maps to chromosome band 22q12. The NF2 is caused by a “de novo” mutation at 22q12 in more than 50% of patients. It is a tumor suppressor gene with a molecular weight of 110 kb, it consists of 16 consecutive exons and alternatively spliced exon. The protein encoded by NF2 gene is called Merlin. The Merlin has a similar structure to the family of proteins that link cell surface glycoproteins to actin cytoskeleton. The most important finding for the diagnosis of NF2 is the presence of bilateral schwannomas involving the eighth cranial nerve, with an incidence of about 95% of patients. Individuals with NF2 also have an increased risk of developing single or multiple meningiomas and schwannomas of peripheral nerves^[1].

SCHWANNOMATOSIS

A small subset of patients with multiple schwannomas without any clinical signs and without any radiological evidence of vestibular lesions or other characteristic features of NF2 has been identified.

The genetic and molecular analysis performed on the tumors of these patients, revealed that it is possible to frame schwannomatosis as distinct clinical and genetic syndrome. Schwannomatosis is defined, therefore, as an extremely rare tumors syndrome characterized by the presence of multiple schwannomas in the absence of typical signs of NF1 and NF2 syndromes. Usually, patients with schwannomatosis develop cranial, spinal or peripheral nerve schwannomas but do not develop vestibular lesions (VS), typical of NF2. Moreover, even the genetic features are different respect to neurofibromatosis, allowing to classify the disease as a distinct nosological entity.

Diagnosis

An important aspect for the classification of Schwannomatosis is the differential diagnosis with NF. In particular, we can define Schwannomatosis a syndrome characterized by multiple schwannomas in the absence of VS, having no characteristic of NF1 or NF2, having no familiarity and, having no constitutional mutations

of specific gene, as like 17q11.1 in NF1 and 22q12 in NF2.

Clinical and radiological: The Schwannomatosis has been described for the first time in the 1973 as neurofibromatosis type 3. The characteristic of this syndrome was the presence of multiple skin and spinal's schwannomas in the absence of vestibular involvement or other relevant features of NF1 and NF2. Over time, several authors have reported cases of patients with multiple schwannomas without vestibular lesions, suggesting the existence of a distinct syndrome from the NF. Patients with schwannomatosis develop multiple schwannomas on cranial, spinal and peripheral nerves, but they do not develop vestibular schwannomas. The locations of the schwannomas included intraspinal (multiple sites), paraspinal, brachial plexus, femoral nerve, sciatic nerve, calf, forearm, retroperitoneum, and middle cranial/infratemporal fossa region. The prevalence in the cervical inferior tract and the dorso-lumbar passage is interpreted by the authors as being related to the presence of a higher concentration of roots and directed to the superior and the inferior limbs at those levels. The mean duration of symptoms ranges between 2 and 3 years. The common presenting symptoms included paresthesias, pain, weakness, or palpable mass. Usually the growth of the tumor was very slow, and the symptoms that were vague in the beginning worsened very slowly. The age of its first manifestation was usually, with exception to few cases and few sites, around the 3th and 4th decade. No prevalence between male and female was found.

At this time there are no NIH diagnostic criteria for schwannomatosis. Jacobi *et al* have proposed clinical criteria for diagnosis of schwannomatosis: the presence of two or more schwannomas in the absence of radiological evidence of vestibular lesions in patients older than 18 years, is definitely indicative of schwannomatosis. Michael *et al* have proposed an integration of these diagnostic criteria, indicating the MRI exam as a fundamental instrument to exclude the presence of vestibular schwannomas and, more important is the absence of constitutional NF2 mutations. Today, therefore, the first major challenge to the diagnosis of schwannomatosis is the presence of two or more non-intradermal schwannomas in patients older than 30 years, in the absence of vestibular lesions shown on the brain MRI with contrast enhancement and in the absence of constitutional NF2 mutations. Second important aspect is the presence of first-degree relative with a confirmed diagnosis of schwannomatosis in a patient with multiple schwannomas in the absence of vestibular lesions resulting on MRI imaging and genetic analysis, in this case, without any limit of age.

The electromyographic diagnosis is needed to determine with certainty the origin of the lesion by a motor root and evaluate the extent of any damage.

Molecular genetics; Several authors have studied the schwannomatosis molecular genetics. Jacobi and McCollins analyzed alterations in the NF2 locus in patients with schwannomatosis revealing in the tumor cell, a typical truncating mutations at NF2 gene, with loss of heterozygosity of chromosome 22. They found that unlike patients with NF2, no heterozygous NF2 gene changes were seen in normal tissues. They identified 20 different somatic mutations in the NF2 gene, 18 of which were truncating mutations. None of the mutations detected in tumour specimens was detected in paired blood specimens. Lymphocyte DNA did not reveal any NF2 mutation but the tumour DNA showed loss of heterozygosity and mutations of NF2 gene. Tumors from these patients frequently had the same truncating mutations and loss of heterozygosity at the NF2 locus as NF2 patients. However, normal tissue did not contain these changes, implying that the underlying genetic mechanism of NF2 and schwannomatosis differs. They concluded that schwannomatosis is a

distinct entity from type 2 neurofibromatosis.

The SMARCB1 gene has been found to harbor germline alterations in both familial and sporadic schwannomatosis patients. Several linkage studies performed in families affected with schwannomatosis excluded NF2 as the germline-transmissible schwannomatosis gene and suggested a location of this gene near marker D22S1174, which is in the region on chromosome 22 centromeric to NF2. In this region is the CABIN1 (also known as SMARCB1) gene, in which missense mutations may contribute to the pathogenesis of both schwannomatosis and NF2. INI1 is an attractive candidate gene, because it is a tumor-suppressor gene that is located within a short distance (i.e., <360 kb) of marker D22S1174 [University of California Santa Cruz (UCSC) Genome Browser]. INI1 is a member of the ATP-dependent SWI-SNF chromatin remodeling complex and affects the expression of genes that regulate cell cycle, growth, and differentiation. However further studies are needed to determine whether the inactivation of the INI1 gene is the cause of

tumor formation in cases of familial and sporadic schwannomatosis as well and to elucidate the exact oncogenic mechanisms and functional consequences of INI1 inactivation in these and other tumors. Surely as germline SMARCB1 mutations have never been reported in cases of vestibular schwannomas, the presence of multiple non-vestibular schwannomas appears a good criterion to first investigate the SMARCB1 gene

Treatment

The treatment in case of symptomatic lesions is surgical removal; Asymptomatic tumours can be monitored conservatively with serial MRI studies. The surgical approach is usually due to back and can be performed using classical laminectomy or, more frequently in young patients with laminotomy in order than to restore the correct anatomical integrity of the spine. The approach to the lesion provides, in cases of intradural lesions, the execution of a median durotomy which allows exposure of the roots and the spinal cord. In most cases schwannomas originate from the sensory root, for which their localization within the spinal canal is almost always posterolateral. In rare cases, however, the origin is from the motor root resulting in more anterior localization. The removal, in order to prevent recurrence, must be total and possibly en bloc. In cases where the origin is from the sensory root, removal, after careful dissection of the adjacent neural structures, occurs through the section of the sensory root of origin. Clearly the same can not be executed in case of origin from motor root. Only for thoracic motor roots is indicated resection of the root. The procedure is always performed with micro-surgical technique through the use of the surgical microscope. Another extremely important tool is ultrasonic aspirator CUSA, which allows the surgeon to a fragmentation and an aspiration of the lesion, performing a debulking of the lesion from the inside. In all cases, in our opinion, it is imperative to run during the surgical procedure, intraoperative neurophysiological monitoring, in order to make the procedure more safe. In cases where the lesion has efflux intra-extraforaminal, for its removal may be necessary to remove the articular mass to reach the intervertebral foramen and the extraforaminal portion; in such cases it may be necessary to run an additional instrumented spine stabilization procedure in order to correct the instability generated by the bone removal. The complete removal of the tumor is the ultimate goal; in fact, in our case reports, which confirmed other reported series, the recurrence occurred in all the cases in which the excision was subtotal. Radiation therapy is indicated in some cases of subtotal removal and malignant lesions.

In any case, given the high incidence of developing additional lesions in patients with Schwannomatosis, it remains imperative, for all patients, to perform serial MRI studies during follow-up time, usually at a yearly interval. It is important to consider genetic testing. Molecular diagnosis rules out NF2 and appropriate genetic counseling can be offered. Patients are advised to monitor themselves for any new neurological problems.

CONCLUSIONS

The genetic and molecular analysis of the tumors described in this article, revealed that it is possible to frame Schwannomatosis as distinct clinical and genetic syndrome from NF syndrome, and this is the real innovation about this pathology, because since now the differential diagnosis was essentially clinical. The treatment in case of symptomatic lesions is surgical removal; in case of asymptomatic lesions is important, instead, to perform serial MRI studies. Given the high incidence of developing additional lesions in patients with Schwannomatosis, it remains imperative to perform serial brain and spinal cord MRI studies during follow-up time. Important is the differential diagnosis including clinical and radiological criteria plus molecular genetic analysis of tumor cells and lymphocyte DNA. Due to the recent molecular and genetic innovations, in the next few years we expect that advances in the research will provide us the use of new potential drug therapies; this to reserve the surgical therapy only in selected cases.

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