THREE YEARS STUDY OF SCHWANNOMAS OF PERIPHERAL NERVES
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ABSTRACT

BACKGROUND
In this paper authors present three cases of schwannomas including a case of multiple schwannomas without the features of neurofibromatosis (NF). There was no family history of neurofibromatosis. All the patients underwent surgical excision and improved from the symptomatic lesions. Histopathology confirmed these lesions as schwannomas. The authors recommend surgery for symptomatic lesions. Asymptomatic tumours can be monitored. Regular follow up is essential as they may develop fresh lesions at any time. The relevant literature is discussed.

• Malignant transformation of the schwannomas is rare and has poor prognosis. It should be considered in the differential diagnosis of schwannomas.
• We should distinguish between “ancient schwannoma” and malignant transformation of schwannoma since treatment and prognosis vary.
• Imaging is not entirely reliable in differentiating benign from malignant peripheral nerve tumours.

MATERIALS AND METHODS
All the patients underwent surgical excision and improved from the symptomatic lesions. Histopathology confirmed these lesions as schwannomas. The authors recommend surgery for symptomatic lesions.

RESULTS
The histopathological studies confirmed the lesion as Flexi Schwannoma and surgery was considered to be the best option.

CONCLUSION
Schwannomas and meningiomas are usually benign tumours curable by complete removal. They occur either as single sporadic tumors in otherwise healthy individuals in the fourth to sixth decades of life or as multiple tumours at an early age as part of the autosomal dominant genetic disorder neurofibromatosis 2 (NF2). The hallmark feature of NF2 is bilateral vestibular schwannomas. Multiplicity, a lobular growth pattern, and invasiveness are typical features of NF2 schwannomas. The diagnosis of NF2 is difficult in a group of heterogeneous and poorly defined patients who do not have BVSs but present with other features suggestive of NF2, namely (1) multiple meningiomas or schwannomas and/or (2) meningiomas (s) or schwannomas (s) in their relatives. These cases are uncommon and they present problems for prognosis, therapy, follow-up, and genetic counseling.

KEYWORDS
Schwannoma, Schwannomatosis, Cafe-au-Lait Spots, Peripheral Nerve Neoplasm, Molecular Genetics, Treatment Outcome, Sciatic Nerve, Malignant Transformation, Malignant Peripheral Nerve Sheath Tumor.

HOW TO CITE THIS ARTICLE: Dhua S. Three years study of schwannomas of peripheral nerves. J. Evid. Based Med. Healthc. 2017; 4(14), 820-827. DOI: 10.18410/jebmh/2017/158

BACKGROUND
The benign tumours of peripheral nerves include schwanna, neurofibroma and perineurioma, the first two being the most common.¹,²,³ Malignant transformation of schwannomas is extremely rare.⁴ Malignant peripheral nerve tumours are commonly referred to as malignant peripheral nerve sheath tumours (MPNST) and are primary malignant sarcomas originating from peripheral nerves or extra neural soft tissues that show nerve sheath cell differentiation.¹,³,⁴ Schwannomatosis was first reported in 1973 as neurofibromatosis type 3.⁵ Multiple cutaneous and spinal schwannomas, without acoustic tumours or other signs of NF1 or NF2, is characteristic. Peripheral nerve tumours are rare conditions. They arise from the nerve sheath, which in turn originates from the neuroectoderm and neural crest. Schwannomas are the most common peripheral nerve sheath tumours.⁶ Multiple schwannomas in the same individual may suggest neurofibromatosis type 2.⁷ Two-thirds of NF2 affected individuals will develop schwannomas and they may precede vestibular tumours. There are reports of individuals with multiple schwannomas who do not show evidence of VS vestibular schwannomas (VS). or other features of NF2.⁸,⁹ They suggest that Schwannomatosis is distinct from other forms of neurofibromatosis. Schwannomas most commonly occur in adults between 20

Financial or Other, Competing Interest: None.
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DOI: 10.18410/jebmh/2017/158

and 50 years of age in both sexes. They generally affect the main trunk of the nerve, more specifically in the upper limb. The posterior tibial nerve at the tarsal sinus is the most frequently involved nerve of the lower limb. Multiple schwannomas is a rare entity not necessarily correlated with neurofibromatosis, which demonstrates very precise chromosomal alterations.\textsuperscript{10,11}

<table>
<thead>
<tr>
<th>Schwannomas</th>
<th>Neurofibroma</th>
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<tbody>
<tr>
<td>Are solitary, well-circumscribed, encapsulated tumours, eccentrically located on nerve roots</td>
<td>Multiple, lack tumor capsule</td>
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<tr>
<td>From proximal nerves or spinal nerve roots.</td>
<td>From distal nerves, causing fusiform enlargement of distal nerves</td>
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<tr>
<td>Arise from a single fascicle, and grow displacing circumferentially the other fascicles within the nerve sheath,</td>
<td>Arise from perineural fibrocytes, cells having many histological similarities to Schwann cells.</td>
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<tr>
<td>Originate from the sensory fascicles in mixed nerves</td>
<td>Arise from motor component of the nerves</td>
</tr>
<tr>
<td>Fascicular bundles are NOT more intimately involved</td>
<td>Fascicular bundles are more intimately involved</td>
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Differential diagnoses include rare nerve tumours that might develop from the constitutive elements of the nerve such as

- intra-nervous lipoma,
- haemangiomta of Schwann's sheath and - Neurofibrolipoma.
- Mucoid cysts are rare and
- Benign tumours which can arise from all peripheral nerves near joints and which should be suspected when facing rapid occurrence of neural lesion near joints. Pre and postoperative search for communication with the neighbouring joint should be performed especially to reduce the risk of recurrence.\textsuperscript{12,13}

**MATERIALS AND METHODS**

The Patient Summary-

<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Sex</th>
<th>Presenting Symptoms</th>
<th>Tumour Distribution</th>
<th>Clinical findings</th>
<th>Surgery</th>
<th>Pathology</th>
<th>Family History</th>
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<tr>
<td>1</td>
<td>18</td>
<td>F</td>
<td>swelling on the lower lip, which was insidious in onset and gradually progressive</td>
<td>lower lip</td>
<td>Physical examination revealed a slow growing, smooth surfaced and nontender mass measuring 3 cm × 3 cm located in the vermilion area of the lower lip [Figure 1]. There was no history of discharge or pain. Laboratory test results revealed peripheral hypercellular (Antoni A) and central hypocellular (Antoni B) regions. Fibroma, neurofibroma, plexiform schwannoma, leiomyoma, minor salivary gland tumour and other benign mesenchymal tumours were considered in the differential diagnosis of this mass of the lower lip.</td>
<td>The mass was excised under local anaesthesia. It was an encapsulated tumour mass measuring 3 cm × 3 cm, with a fairly firm and smooth surface. Figure 3. The postoperative view immediately after surgery is presented in Figure 2, and full recovery was evident 6 weeks after surgery.</td>
<td>The histopathologic studies of the tumour mass showed typical Verocay bodies composed of palisading nuclei and surrounding spaces filled with eosinophilic filaments in Antoni A area. No necrosis was noted and there were no atypical mitotic figures. In Antoni B region, a closely textured matrix with areas of oedema, myxomatous changes, cystic degeneration, and dilated vessels were noted. On the basis of histopathologic findings and immunohistochemical profile, a diagnosis of plexiform schwannoma was arrived at [Figure 5 &amp; 6].</td>
<td>No family history</td>
</tr>
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Multiple swelling in the left side of back, side of the chin, right side of knee, back of the knee with tingling sensation in the back portion of right leg.

MRI D-SPINE Findings: known case of multiple intradural schwannoma. Operated case of L2 and D10-D11 intradural lesions. Comparison made with prior MR scans. Present scan shows multiple well defined oblong intensely enhancing T2 hyperintense intradural extramedullary lesions at C7, D2, D7, D11-D12, L1, L2, L3 levels causing mass effect on the cord, however, no evidence of cordmyelomalacic changes. Largest lesion measures 3.9 (cc) x 1.2 (ap) cm at C7-D2 level – seen causing significant mass effect on the cord which is displaced anterolaterally towards left side.

Multiple surgeries for schwannomas in different locations performed during 3-22005, 25-5-2006, 4-32010, 16-32011 and in March 2015. Radiological investigation of March 2015 showed multiple intradural schwannoma. Mases were excised at different intervals since 2005 Figure 7

The histopathological studies confirmed diagnosis of plexiform schwannoma.

Father was operated for spinal tumour in cervical region 23 years back. A vertical scar in midline in back, thoraco-lumbar region 15 cm & 5 cm each.

In Figure 1 the photograph of the Plexiform Schwannoma of the lower lip is presented and in figure 2 the post-operative view of the lip after six weeks of surgery is presented to show the significant improvement in the appearance of the lower lip of the patient.

![Figure 1. Plexiform Schwannoma of the Lower Lip](image1)

![Figure 2. Post-Operative View of the Lip Weeks After Surgery](image2)
In figure 3 and 4 the encapsulation of the tumor with the Plexiform Schwannoma tissue is shown.

**Figure 3.** Scanner view (4x) – Micrograph Showing Each Module Encapsulated by thin Fibrous Septae. found in the Lip

**Figure 4.** Encapsulation of the Tumour with the Plexiform Schwannoma Tissue of the Thigh

**Histological Studies**

**Histological and radiological distinction between schwannomas and neurofibromas**

Histological features of schwannoma may include areas of compact bundles of Schwann cells (Antoni type A) or loose matrix of oval cells (Antoni type B). Antoni A areas show greater cellularity in schwannomas compared to neurofibromas. S-100 immunostaining is particularly prominent and uniform in cellular areas of the schwannomas, whereas neurofibromas tend to be variable in staining of cells for the S-100 protein. This characteristic is also useful when differentiating schwannomas from fibrosarcoma and leiomyosarcoma. T2-weighted MRI may show peripheral hyper intense rim with central low intensity. This is the “target pattern” which is characteristic of schwannoma on contrast-enhanced T1-weighted and T2-weighted images.

Histopathological Slides are Presented in Figure 5 and 6.

**Figure 5.** Scanner view (4x) - Micrograph Showing each Module Encapsulated by Thin Fibrous Septae.

**Figure 6.** High Power View (40X) – Showing Nuclear Palisading (Veroey Bodies) and Individual Cells are Narrow, Elongated, Wavy with Tapered Ends.
MRI Investigations
Multiple well defined oblong intensively enhancing T2 hyper intense intradural extra medullary lesions at C7-D2, D11-D12, L1, L2&L3 levels largest lesion at C7-D2 level.

Plexiform Schwannoma in the leg
Plexiform Schwannoma in the leg in figure 8 and figure 9 is shown in the posterior aspect and in figure 9 shown removal of the tumour. In figure 10 is presented encapsulation of popliteal fossa region of the leg tumour with Plexiform Schwannoma tissue.

Figure 8. Swelling in the posterior aspect and popliteal fossa region of leg.

Figure 9. The tumour is being removed

Figure 10: Encapsulation of Tumour with Plexiform Schwannoma Tissue
Molecular Pathology 5
The Section of Molecular Pathology (MPA) conducts original research to study the molecular basis and a genetic pathway of human neoplasms. MPA is also responsible for the World Health Organization (WHO) Blue Book's consensus tumour classification. Recently, molecular markers are increasingly being used to define disease entities, taking advantage of rapid progress in the understanding of the genetics of human neoplasm. Alterations in the NF 2/LAT S1/LAT S2/YAP pathway has been identified in schwannoma development. Schwannoma is a benign nerve sheath tumour composed of well-differentiated Schwann cells with 50–60% NF2 mutations. The molecular basis of schwannomas is not fully understood. LATS1 and LATS2 are downstream molecules of NF2 and negative regulators of the YAP oncogene in the Hippo signalling pathway. In a series of 82 sporadic schwannomas mutations of the NF2, LATS1, and LATS2 genes, promoter methylation of LAT S1 and LATS2, and expression of YAP and phosphorylated YAP (pYAP) were analysed and the following conclusions were reached.

- Targeted sequencing using the Ion Torrent Proton instrument revealed NF2 mutations in 45 (55%) schwannomas, LATS1 mutations in 2 (2%) schwannomas, and LATS2 mutations in 1 (1%) schwannoma.
- Methylatation-specific polymerase chain reaction (PCR) showed promoter methylation of LATS1 and LATS2 in 14 (17%) and 25 (30%) cases, respectively.
- 62 (76%) cases had at least one alteration in the NF2, LATS1, and/or LATS2 genes.

Immunohistochemistry revealed nuclear YAP expression in 18 of 42 (43%) and reduced cytoplasmic pYAP expression in 15 of 49 (31%) schwannomas analysed, all of which had at least one alteration in the NF2, LATS1, and/or LATS2 genes. These results suggest that an abnormal Hippo signalling pathway is involved in the pathogenesis of the majority of sporadic schwannomas.14,15

NF2 Tumor Suppressor Gene and Merlin (Schwannomin)
The presence of a tumor suppressor gene on chromosome 22 was identified due to the loss of heterozygosity in NF2, sporadic meningiomas and schwannomas. This was confirmed by the molecular genetic analysis of a large series of NF2 pedigree that demonstrated linkage of NF2 to chromosome 22q12.16,17,18 Studies confirmed NF2 Germline mutations in individuals affected with NF2. Identification of numerous somatic mutations in both NF2 and sporadic schwannomas and meningiomas, confirming the hypothesis of the NF2 gene functioning as a tumor suppressor.19,20,21

The NF2 gene product, merlin (moesin-ezrin-radixin-like protein; Schwannomin), is a 595- amino acid protein belonging to the protein 4.1 superfamily which includes moesin, ezrin, radixin, erythrocYTE protein 4.1, talin, and several tyrosine phosphatases. Ezrin, radixin, and moesin (the ERM family) are cytoskeleton-associated proteins that act as structural links between the cytoskeleton and the plasma membrane.22

At least two major alternatively spliced merlin variants are expressed in vivo55.
- Isoform 1, encoded by exons 1-15 and 17, has intramolecular interactions similar to those of ERM proteins;
- Isoform 2, encoded by exons 1-16, probably exists only in an unfolded state. Merlin is expressed mainly in the nervous system, including Schwann cells, neurons, astrocytes, and cells of the lens.23,24

The growth-inhibiting activity of merlin seems to depend on the formation of intramolecular complexes and that the growth-regulating effects of merlin may be due to alterations in cytoskeletal function.25 Thus it is a unique type of tumor suppressor.

Multiple Schwannoma of Sciatic Nerve
Schwannomatosis was previously described as a distinct, non-hereditary condition. Mac-Collin et al8 suggested that Schwannomatosis might be due to segmental mutation of the NF2 gene or other schwannoma-related genes. Evans et al22 showed that linkage analysis in families with Schwannomatosis was consistent with involvement of the NF2 gene. Honda et al23 found germline mutation in patients who presented with Schwannomatosis who subsequently developed others signs of NF2. Single schwannoma is a rare benign tumour of nerve sheath cells, but it is the most common of all peripheral tumours. Multiple localized schwannomas confined to a deep, major nerve in a single extremity is rare. Lewis et al. described a patient with 12 tumours along the median and ulnar nerves. Shank et al25 presented a case with 4 to 6 schwannomas in the right ulnar nerve. Ogose et al26 presented a case series with 4 patients all with multiple schwannomas arising from peripheral nerves in a single extremity. Mac-Collin also presented a series with 3 patients having multiple tumours limited to a single limb. Most patients in this series presented with pain. Pain was relieved post-surgical removal of tumour. Schwannoma is an encapsulated, slow growing nerve sheath tumour. Neurofibroma does not possess a true capsule. Schwannoma is the most common of all peripheral nerve tumours.

Inclusion and Exclusion Criteria
Schwannomatosis has been described distinct clinical entity with an unresolved the genetic background. Its occurrence in families is still unknown. The patient with schwannomatosis typically has multiple spinal, peripheral nerve, or subcutaneous schwannomas, without BVSs, and the disease is segmental or localized to a certain body part in approximately one-third of patients. Schwannomatosis is rarely seen as a familial condition, often showing incomplete penetrance, which is in distinct contrast to NF2. Most patients with schwannomatosis are middle aged at presentation and clearly older than NF2 cases. Genetically, Schwannomatosis may include patients with: (1) a clinically very mild NF2; (2) segmental NF2; (3) or those with a
putative modifier gene defect on chromosome 22q, making
the NF2 gene susceptible to mutations without germ-line
inactivation. Jacoby et. Al27 has proposed the following
diagnostic criteria for schwannomatosis.

**Definite Schwannomatosis**
1. Two or more schwannomas confirmed by
   histopathology plus.
2. Lack of radiographic evidence of vestibular
   schwannoma, at age >18 years.

**Presumptive or Probable Schwannomatosis**
1. Two or more histopathologically diagnosed
   schwannomas, without symptoms of eighth nerve
dysfunction, and age >30 years, or
2. Two or more histopathologically verified schwannomas
   in an anatomically limited distribution (single limb or
   segment of the spine), without symptoms of eighth
   nerve dysfunction, at any age.

**DISCUSSION**
The first criterion for definite schwannomatosis is fulfilled if
the patient has two or more nonintradermal schwannomas,
is older than age 30 years, lacks evidence of VS on high
quality MRI scan and does not have a known constitutional
NF2 mutation. The second criterion for definite
schwannomatosis is fulfilled if an individual has a first degree
relative with definite schwannomatosis and has one or more
pathologically confirmed non-VS schwannomas, without
reference to the patients’ age, MRI scan results, or results
of NF2 mutation testing. Evans et al reported five families
with schwannomatosis inherited in an autosomal dominant
pattern. They had multiple skin and spinal schwannomas
without vestibular tumors. One member of a sixth family
who initially appeared to have schwannomatosis, developed
bilateral acoustic neuromas and was later classified as
having NF2. He noted difficulty in distinguishing the two
disorders and suggested that young patients with multiple
schwannomas may have a variant of NF2. Currently, there
are no NIH diagnostic criteria for schwannomatosis. Jacoby
et al proposed clinical criteria for the diagnosis of
schwannomatosis. They suggested two or more
pathologically proven schwannomas and lack of radiographic
evidence of vestibular tumors at age more than 18 years
could be taken as evidence of definite schwannomatosis. If
MRI of the brain is not available then a probable or
presumptive diagnosis may be made if the patient has two
or more pathologically proven schwannomas and no clinical
symptoms of eighth nerve symptoms at age greater than 30.
Michael et al proposed modifications that increase the
specificity of schwannomatosis diagnostic criteria. According
to these authors all patients with definite or possible
schwannomatosis must not fulfil any of the existing criteria
for NF2 and have no evidence of VS on high quality MRI
scan, no first degree relative with NF2 and no constitutional
NF2 mutations. Malignant transformation of schwannomas
is rare. The term ancient schwanna, which is not an
indicator of malignancy, is used to describe an old
schwannoma that has undergone degenerative changes
over time (this variant of schwannoma is also rare).
Degenerative changes that characterize an ancient
schwannoma include interstitial hyalinization, cyst
formation, calcification and haemorrhage, along with
degenerative nuclear atypia, but without any mitotic activity.

**CONCLUSION**
Schwannomas and meningiomas are usually benign tumours
curable complete removal. They occur either as single
sporadic tumours in otherwise healthy individuals in the
fourth to sixth decades of life or as multiple tumours at an
early age as part of the autosomal dominant genetic disorder
neurofibromatosis 2 (NF2). The hallmark feature of NF2 is
bilateral vestibular schwannomas. Multiplicity, a lobular
growth pattern, and invasiveness are typical features of NF2
schwannomas. The diagnosis of NF2 is difficult in a group of
heterogeneous and poorly defined patients who do not have
BVSs but present with other features suggestive of NF2,
namely (1) multiple meningiomas or schwannomas and/or
(2) meningiomas (s) or schwannomas (s) in their relatives.
These cases are uncommon and they present problems for
prognosis, therapy, follow-up, and genetic counseling.

**REFERENCES**
[1] Sundaram C, Mahadevan A. Tumours of cranial and
peripheral nerves. In: Tandon PN, Ramamurthi R, eds.
Ramamurthi and Tandon's textbook of neurosurgery.
Vol. 2. 3rd edn. New Delhi: Jaypee Brothers Medical
Publisher 2012:1446–1452.
[2] Mrugala MM, Batchelor TT, Plotkin SR. Peripheral and
peripheral nerve sheath tumors: diagnostic overview and
[4] Woertler K. Tumors and tumor-like lesions of
multiple du nerf sciatique. À propos d'un cas. Rev Chir
[7] Gutman DH. Molecular insights into neurofibromatosis
line mutations in the neurofibromatosis 2 gene:
correlation with disease severity and retinal
schwannoma of the sciatic nerve originating in a spinal
plexiform neurofibroma associated with


