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# MRI in Evaluating Neurocutaneous Syndromes: A Retrospective Analysis

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**Abstract**

Neurocutaneous syndromes are a group of genetic disorders that arise primarily from the neuroectoderm. Besides the central nervous system (CNS), these syndromes also impact the peripheral nerves, skin, connective tissue, and various other organ systems. They require a multidisciplinary approach as early diagnosis and intervention are crucial to managing complications and improving quality of life.

This study illustrates how MR imaging is indispensable in the management of neurocutaneous syndromes, enabling early diagnosis, accurate characterization, and ongoing monitoring of disease manifestations. It plays a pivotal role in guiding clinical decisions and improving patient outcomes.

**Keywords:** Neurocutaneous Syndromes, Neurofibromatosis 1 And 2, Tuberous Sclerosis, Sturge Weber Syndrome, Von Hippel Lindau Syndrome.

## Introduction

Neurocutaneous syndromes also known as phakomatoses, are a diverse collection of congenital abnormalities that largely affect tissues originating from the embryological neuroectoderm. In addition to the central nervous system (CNS), these syndromes affect the peripheral nerves, skin, connective tissue, and other organ systems. (1)

They include neurofibromatosis 1 (NF-1), neurofibromatosis 2 (NF-2), tuberous sclerosis (TS), Sturge-Weber syndrome (SWS), Von Hippel-Lindau (VHL) disease, PHACE syndrome, ataxia telangiectasia

(AT), linear nevus syndrome (LNS), hypomelanosis of Ito (HOI), and incontinentia pigmenti (IP). (2)

Out of the above, neurofibromatosis (NF-1, NF-2), VHL, and TS have a higher occurrence of neoplasms, especially the first two, which are characterized by a multiplicity of tumours. Radiologic study offers the potential for early identification of malignancies and enhanced management and prognosis. (3) Clinical neuroradiology is crucial not only for the diagnosis of the type of neurocutaneous syndrome but also during the follow up and monitoring of patients with these syndromes.

Magnetic Resonance Imaging (MRI) is the primary radiological technique, while Computed Tomography (CT) is only employed in rare circumstances. Due to significant differences among the syndromes, imaging techniques must necessary vary. Neuroimaging of the brain usually involves axial FLAIR and T2-weighted sequences, diffusion weighted imaging, and frequently T2-weighted or SWI sequences. (4)

This review demonstrates and delineates the impact that magnetic resonance (MR) imaging has had on the assessment of neurocutaneous syndromes.

**Aim and Objectives**

The aim of this study is to review the role of MRI as a method of imaging to diagnose patients with neurocutaneous syndromes. The objectives are to illustrate and review the MR imaging findings of neurocutaneous syndromes along with their clinical features and common presentations.

**Materials And Method**

The study was conducted across a period of one year in a tertiary healthcare centre in Navi Mumbai, Maharashtra, India. This was a retrospective study done across 18 patients suspected of neurocutaneous lesions. All the scans were performed using a 1.5-T TOSHIBA Magnetic Resonance Imaging scanner. Diagnosis was made based on the typical MR imaging appearances, location and associated features. Patients not diagnosed with neurocutaneous syndromes and those lost on follow up were excluded from the study. Ethical approval was obtained from the Institutional Ethics Committee before the commencement of the study.

**Results**

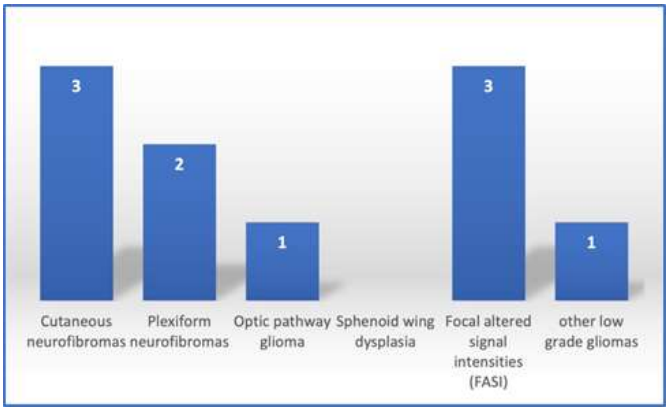
Our study included a total of 18 patients, of which 11 (61.1%) were male and 7 (38.9%) were females of varying ages from 10 months to 41 years where the mean age was 21 years. As illustrated in Table 1, 10 out of 18 cases (55%) were NF-1, 1 (5.5%) was NF-2, 4 (22.2%) were Sturge Weber Syndrome, 1(5.5%) was VHL, 2 (11.1%) were TS.

Table 1: Distribution and classification of various neurocutaneous syndromes

| Diagnosis | Numbers of cases |
|---|---|
| Neurofibromatosis 1 (NF 1) | 10 |
| Neurofibromatosis 2 (NF 2) | 1 |
| Sturge Weber Syndrome | 4 |
| Von Hippel Lindau Disease | 1 |
| Tuberous Sclerosis | 2 |
| Total | 18 |

**Neurofibromatosis Type 1 (NF-1)**

In our study, NF-1 was recognised in 55% (10 out of 18 patients). As seen in Chart 1, cutaneous neurofibromas were present in 30% of our patients, focal altered signal intensities in 30%, plexiform neurofibromas in 20%, optic pathway gliomas in 10% and low grade glioma in 10% patients.




Graph 1: Presentations seen in NF-1

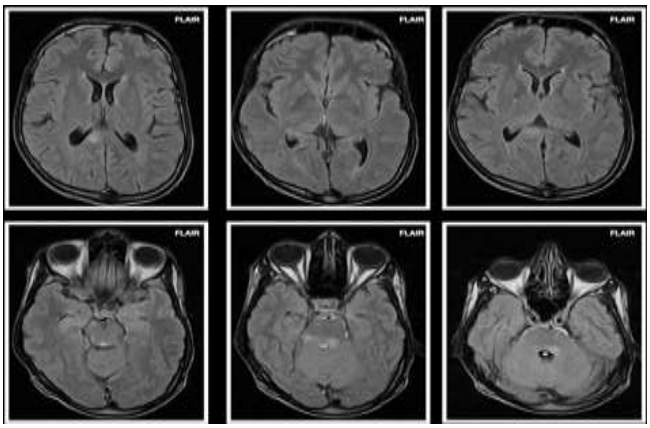


Figure 1a: FLAIR hyperintense signal involving the splenium of corpus callosum on right side, bilateral gangliocapsular regions, midbrain and pons suggestive of Focal Altered Signal Intensities – (FASI) in a case of 22 year old male with Neurofibromatosis 1.

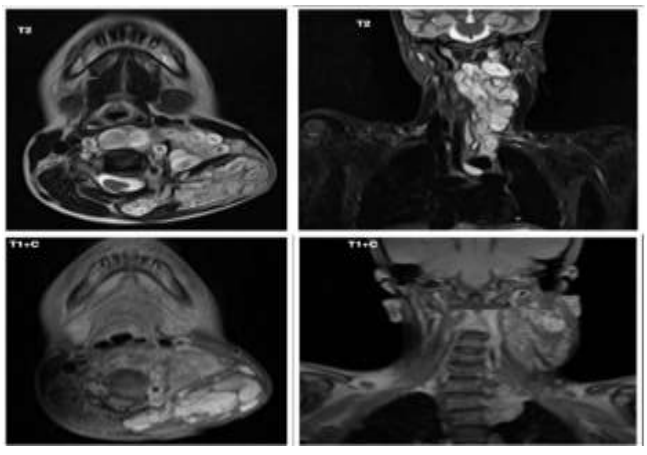


Figure 1b: The same patient showed multiple variable sized, well-defined lobulated lesions on the left side of neck extending from skull base up to the anterior mediastinum involving left paravertebral, paraspinal, carotid, retropharyngeal and pre-vertebral spaces. The lesions appear hyperintense on T2W with central hypointense areas. There is mild to moderate enhancement on post contrast study (PCS).

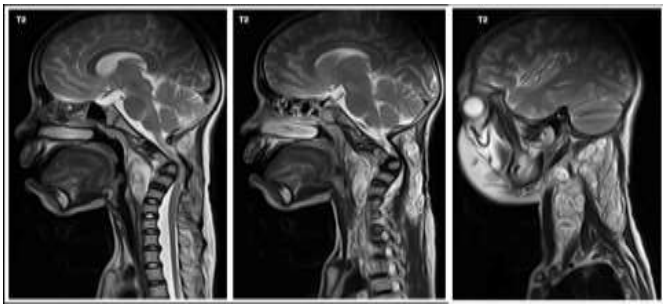


Figure 1c: T2W Sagittal image of the same patient showing severe kyphotic deformity at C2-C4 levels with acute posterior angulation of C3 vertebrae causing significant spinal cord stenosis and cord compression.

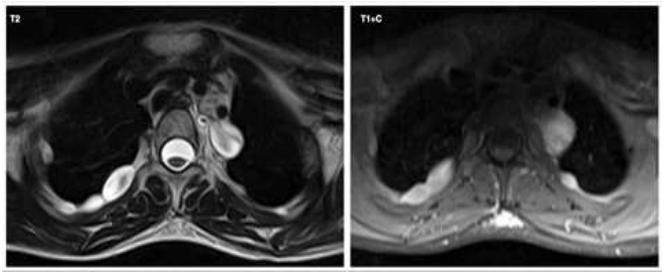


Figure 1d: In these axial images of the same patient, there are T2W hyperintense lesions with central hypointense areas along the posterior aspect of ribs on both sides which shows moderate post contrast enhancement, suggestive of intercostal nerves neurofibroma.

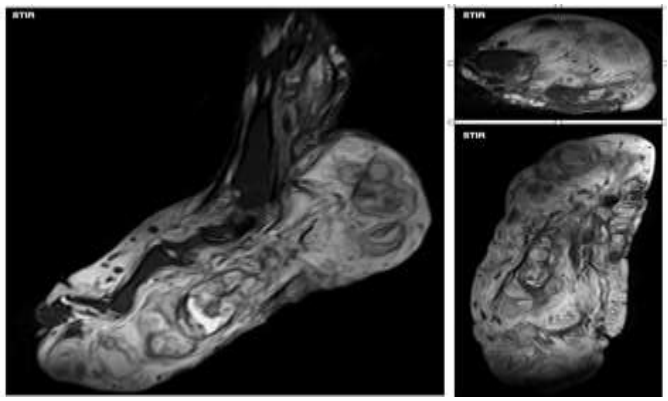


Figure 1e: Diffuse thickening of the subcutaneous plane of foot with multiple variable sized STIR hyperintense lesions with few hypointense areas within representing

plexiform neurofibromas. There is associated destruction of the underlying bones.

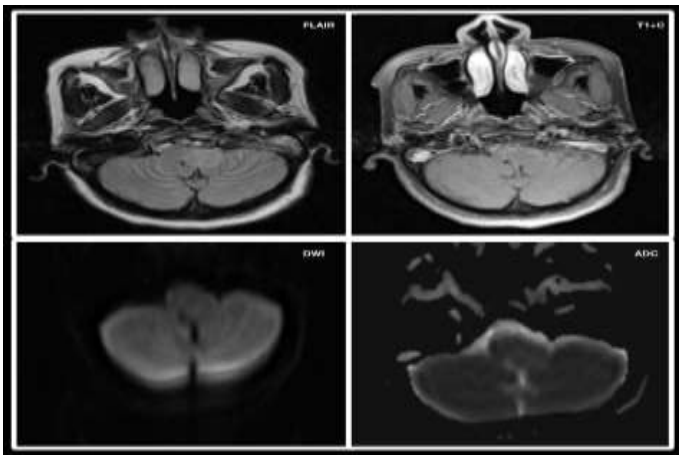



Figure 2: A 40 year old female with Neurofibromatosis 1: Rounded, well-defined, solid, non-enhancing lesion arising from the medulla seen extending into the cerebello-medullary cistern which appears hyperintense on FLAIR and shows no restricted diffusion suggestive of low grade glioma.

**Neurofibromatosis Type 2 (NF-2)**

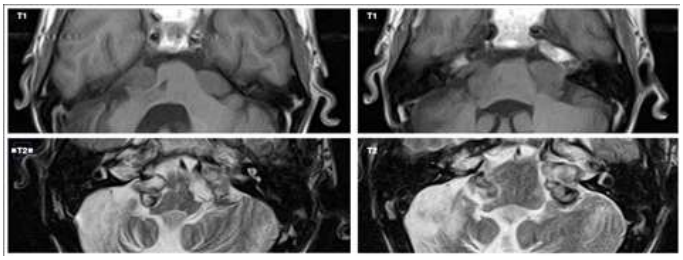


Figure 3: A 24 year old male with Neurofibromatosis 2 showing well- defined extra axial solid lesions involving bilateral cerebello pontine angles extending into porus acousticus representing bilateral acoustic schwannomas.

**Von Hippel-Lindau syndrome**

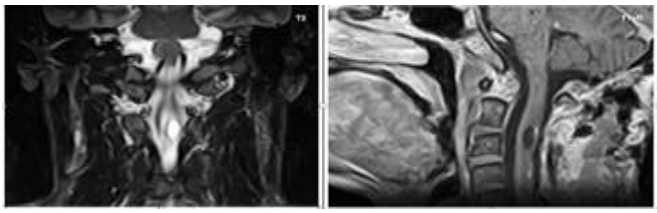


Figure 4a: A 28 year old male with von Hippel Lindau disease showing cystic lesion with a mural hyper enhancing nodule in the posterior aspect of upper cervical spinal cord. There are two other hyper enhancing nodules in the posterior aspect of spinal cord just below this lesion. These are hemangioblastomas involving spinal cord.

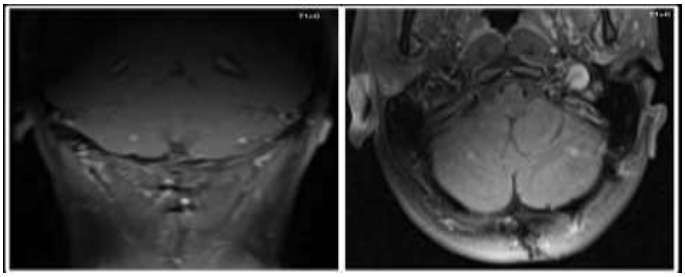


Figure 4b: Same patient showed hyper enhancing nodules in bilateral cerebellar hemispheres representing cerebellar hemangioblastomas.

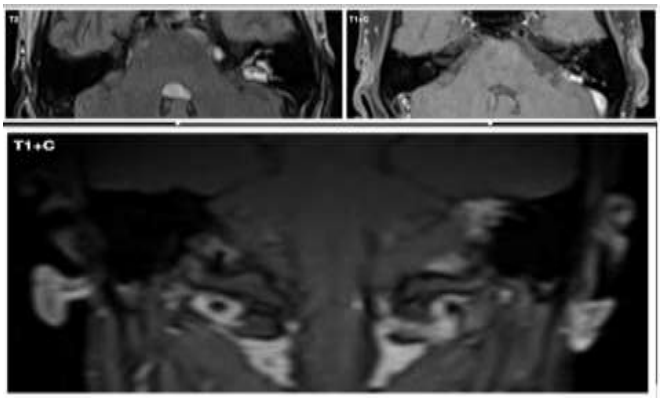
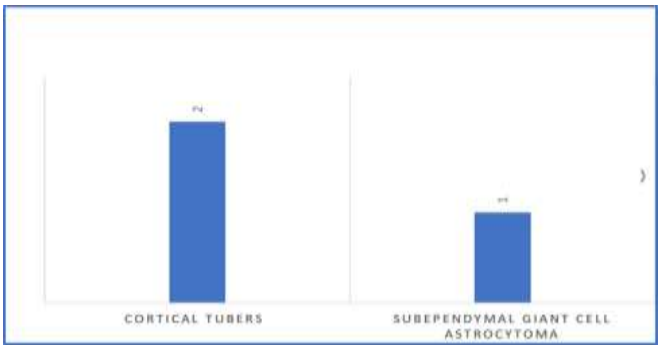



Figure 4c: In these axial images of the same patient, there is a T2W hyperintense lesion involving the petrous part of the temporal bone on the left side which shows post contrast enhancement, representing endolymphatic sac tumour

**Tuberous Sclerosis (TS)**

As seen in Chart 2, both patients diagnosed with TS showed cortical tubers while only one of them had subependymal giant cell astrocytoma (SEGA).




Graph 2: Presentations seen in TS

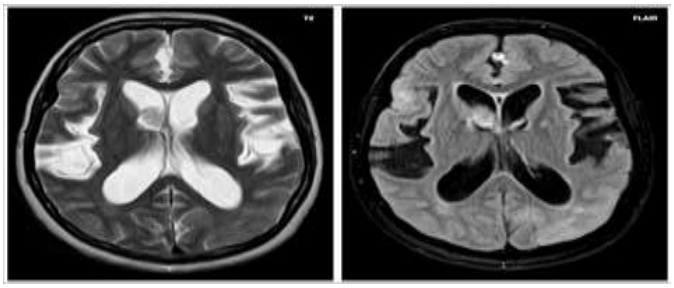
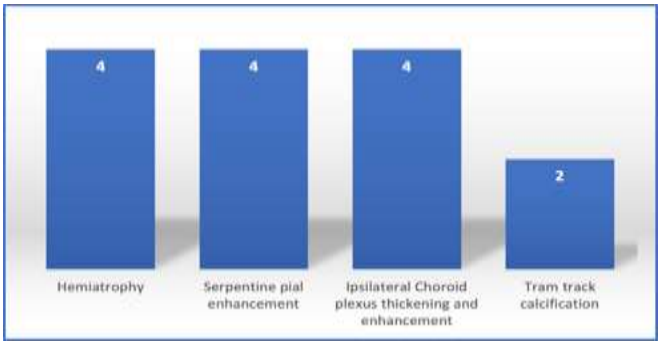


Figure 5: A 40 year old female with tuberous sclerosis: There is a T2W hypointense and FLAIR hyperintense lesion in the frontal horn of right lateral ventricle. In a known case of tuberous sclerosis, it represents subependymal giant cell astrocytoma. Also seen are T2W/FLAIR discrete and confluent hyperintensities involving the cortical and subcortical regions of right frontal and left parietal and occipital lobes, representing cortical and subcortical tubers.

**Sturge Weber Syndrome**

As seen in Chart 3, all patients showed hemiatrophy, serpentine pial enhancement and ipsilateral choroid plexus thickening and enhancement. Two patients also showed tram track like calcifications on GRE images.




Graph 3: Presentation seen in Sturge Weber syndrome

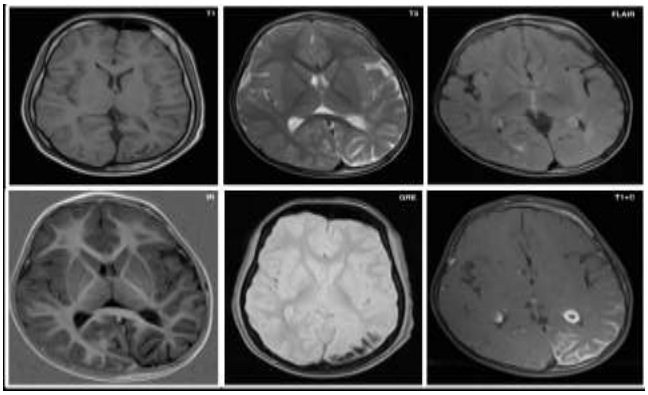


Figure 6: A 2 year old male with Sturge Weber syndrome: Hemiatrophy of the left side with enlarged subarachnoid spaces and subtle FLAIR hyperintensity along the sulci of the left parietooccipital lobes was seen. On inversion recovery (IR) image, volume loss could be appreciated. There is blooming seen on GRE image suggestive of calcification. On post contrast image, there is serpentine pial enhancement along cortical sulci and gyri of left parieto-occipital lobes with thickened and enhancing ipsilateral choroid plexus.

**Discussion**

**Neurofibromatosis Type 1 (NF-1)**

Neurofibromatosis, which was seen in 55 % (10 out of 18) of patients in our study, was first described by Von Recklinghausen over a century ago, is recognized to have up to eight distinct clinical subtypes, with Neurofibromatosis Type 1 (NF-1) and Type 2 (NF-2) comprising over 99% of cases.

NF-1, also known as Von Recklinghausen's Disease, is characterized by multiple skin lesions, central nervous system (CNS) tumours, and mesodermal dysplasia. (5) It is an autosomal dominant condition with an incidence of approximately 1 in 3,000, caused by mutations on chromosome 17. NF-1 exhibits high penetrance and variable expressivity; notably, around 50% of affected individuals may have mutations without a family history. This condition is not uniform and can present in various forms.

CNS manifestations occur in 15-20% of NF-1 patients, significantly increasing the risk of CNS tumors compared to the general population. The most frequent brain abnormality in NF-1 is optic pathway gliomas, affecting about 30% of individuals. These tumors can appear as localized masses or as diffuse enlargements along the optic nerve, with T2-weighted MRI revealing high signal areas, often indicating posterior extension into the optic chiasm and tracts. The most common type of gliomas is juvenile pilocytic astrocytoma, although other glioma grades can also occur. Additional CNS abnormalities include characteristic foci of increased signal intensity (FASI), present in about 75% of NF-1 patients, typically found in the pons, cerebellar white matter, internal capsule, and splenium. These lesions usually appear by age 3, increase in size until around age 10 or 11, and then gradually diminish. They are thought to represent hamartomas or abnormal glial cells. Follow-up MRI is advised to distinguish these from low-grade tumors. Other findings may include cranial nerve tumors, bone dysplasias (such as sphenoid wing hypoplasia leading to pulsating exophthalmos), plexiform neurofibromas, and orbital abnormalities like buphthalmos (globe enlargement due to congenital glaucoma), retinal phakomas, and Lisch nodules.

In 2020, an international panel of experts revised the diagnostic criteria, adding new clinical signs and incorporating genetic testing. (Table 2) It is as follows (6):

Table 2: Revised Diagnostic Criteria for NF1

| |
|---|
| A: The diagnostic criteria for NF1 are met in an individual who does not have a parent diagnosed with NF1 if two or more of the following are present: |
| 1. Six or more café-au-lait macules over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in post pubertal individuals. |
| 2. Freckling in the axillary or inguinal region. |
| 3. Two or more neurofibromas of any type or one plexiform neurofibroma. |
| 4. Optic pathway glioma. |
| 5. Two or more iris Lisch nodules identified by slit lamp examination or two or more choroidal abnormalities. |
| 6. A distinctive osseous lesion such as sphenoid dysplasia, anterolateral bowing of the tibia, or pseudarthrosis of a long bone. |
| 7. A heterozygous pathogenic NF1 variant with a variant allele fraction of 50% in apparently normal tissue such as white blood cells. |
| B: A child of a parent who meets the diagnostic criteria specified in A merits a diagnosis of NF1 if one or more of the criteria in A are present. |

**Neurofibromatosis Type 2 (NF-2):**

NF-2 was seen in 5.5% of patients in our study, is marked by the presence of bilateral vestibular schwannomas. NF-2 is linked to a deletion on chromosome 22, is inherited in an autosomal dominant manner, and has an incidence of approximately 1 in 50,000. Skin manifestations are uncommon. Intracranial manifestations in NF-2 include the typical lesions associated with NF-2 include schwannomas of the acoustic and other cranial nerves (especially cranial nerve V and occasionally cranial nerve X), as well as meningiomas. The bilateral vestibular schwannomas typically manifest in the second and third decades of life and may present as cystic formations. Meningiomas are often multiple, frequently found intraventricularly, and tend to exhibit calcification, particularly in the lateral

ventricle. Additionally, the choroid plexus may enlarge and become calcified. (7)

The diagnostic criteria for NF-2 is outlined by the Revised Manchester Criteria (Table 3) and is as follows (8):

Table 3: Revised Manchester Criteria for NF-2

| The presence of any one of the following criteria suggests the diagnosis of NF2: |
|---|
| 1. Bilateral vestibular schwannomas before age 70 years. |
| 2. Unilateral vestibular schwannoma before age 70 years and a first-degree relative with NF2. |
| 3. Any two of the following tumour types: meningioma, nonvestibular schwannoma, ependymoma, or cataract, and a first-degree relative with NF2. |
| 4. Unilateral vestibular schwannoma and a negative result at LZTR1 testing. |
| 5. Multiple meningiomas and: |
| - Unilateral vestibular schwannoma, or |
| - Any two of the following: nonvestibular schwannoma, ependymoma, or cataract. |
| 6. Constitutional or mosaic pathogenic NF2 gene mutation in blood, or by identification of an identical mutation from two separate tumours in the same individual. |

**Von Hippel-Lindau syndrome**

Von Hippel-Lindau syndrome, seen in 5.5% of patients in our study, is an autosomal dominant disorder with incomplete penetrance, caused by a genetic defect on chromosome 3p25-p26. This condition is characterized by the presence of central nervous system tumors, particularly multiple hemangioblastomas, as well as tumors in the abdominal organs. Hemangioblastomas primarily occur in the cerebellum (65%), brain stem (20%), and spinal cord (15%). These tumors are typically well-defined with smooth edges, with two-thirds being cystic and containing a solid component or mural nodule. On T1-weighted MRI, the nodule is isointense to brain tissue, while it appears hyperintense on T2-weighted MRI, often showing flow voids from tumor vessels. The cystic component is hyperintense relative to cerebrospinal fluid (CSF) on T2-weighted images, with the cyst wall rarely enhancing; in contrast, the mural nodule enhances significantly. Solid tumors display intermediate to high signal intensity on T2-weighted MRI and show homogeneous enhancement. Small hyperintense areas in the white matter may indicate subclinical hemangioblastomas, gliosis, or dystrophic changes. (9)

For von Hippel-Lindau patients, annual screening is recommended, which includes enhanced MRI of the brain and spine, as well as abdominal CT or ultrasound for early detection of potentially life-threatening renal and adrenal tumors. Asymptomatic relatives require careful genetic evaluation, and depending on the findings, some may also need annual screening.

The international diagnostic criteria for von Hippel-Lindau (VHL) disease (Table 4) are as follows (10):

Table 4: International diagnostic criteria for VHL

| | |
|---|---|
| Positive family history/ disease-causing VHL variant | 1 vHL-related manifestation |
| Negative family history | 2 hemangioblastoma (CNS or retinal) or at least one hemangioblastoma (retinal and/ or CNS) and a visceral lesion |
| VHL-related manifestations included in | |

| | |
|---|---|
| the criteria: | Retinal hemangioblastoma |
| | CNS hemangioblastoma |
| | Renal cell carcinoma |
| | Pheochromocytoma |
| | Pnet |
| | ELST |
| | Pancreatic cysts |
| | Epididymal cystadenomas |

**Tuberous Sclerosis**

Intracranial manifestations include cortical hamartomas or tubers, found in 95% of patients, predominantly in the frontal lobe. While some tubers calcify, the rate is not well-defined; by age 10, approximately 50% of patients have calcified lesions. On CT, tubers initially appear as lucencies in widened gyri but become harder to detect with age unless calcified. MRI provides better detection across all ages, with lesions showing different characteristics as myelination progresses.

Subependymal nodules, seen in 90% of cases, typically calcify and are located along the ventricular surface of the lateral ventricle. Their imaging characteristics change with age, and they are best visualized on T1-weighted MRI. Up to 15% of TS patients may develop giant cell astrocytomas, which present as enlarging masses near the foramen of Munro, often causing hydrocephalus. White matter lesions are also common, representing disordered neurons and glial cells. Recent studies suggest that linear hyperintensities may connect subependymal nodules to cortical tubers, indicating areas of hypomyelination or gliosis. Cerebellar white matter lesions are found in about 10% of patients.

The diagnostic criteria for Tuberous Sclerosis Complex (TSC) (Table 5) are as follows (11):

Table 5: Diagnostic criteria for TSC

| |
|---|
| • Definite TSC: 2 major features or 1 major + 2 minor |
| • Probable TSC: 1 major + 1 minor feature |
| • Possible TSC: 1 major or 2 minor features |
| Major Features |
| • Identified clinically |
| • ≥ 3 hypomelanotic ("ash leaf") macules (97%) |
| • Facial angiofibromas (75%) or forehead plaque (15-20%) |
| • Shagreen patch (45-50%) |
| • Ungual/periungual fibroma (15%) |
| • Multiple retinal hamartomas (15%) |
| • Identified on imaging |
| • Subependymal nodules (98%) |
| • Cortical tubers (95%) |
| • Cardiac rhabdomyoma (50%) o Renal angiomyolipoma (50%) |
| o Subependymal giant cell astrocytoma (15%) |
| • Lymphangioleiomyomatosis (1-3%) |
| Minor Features |
| • Identified clinically |
| • Gingival fibromas (70%) |
| • Affected first-degree relative (50%) |
| • Pitting of dental enamel (30%) |
| • Retinal achromic patch (35%) |
| • Confetti-like skin macules (2-3%) |
| • Identified on imaging |
| • WM hamartomas, radial migration lines (100%) |
| • Hamartomatous rectal polyps (70-80%) |
| o Nonrenal hamartomas (40-50%) |
| • Bone cysts (40%) |
| • Renal cysts (10-20%) |

**Sturge Weber Syndrome**

Encephalotrigeminal angiomatosis, another name for Sturge-Weber Syndrome (SWS) which was seen in 22.2% of cases in our study, is a congenital vascular disease that affects the leptomeninges, face, and eye choroid. It affects both sexes equally and is usually sporadic in nature; However, some familial cases have been documented. The face lesion known as a facial angioma, or port wine nevus, is the characteristic lesion of SWS and is present from birth while some individuals may not have it. (12)

The best way to detect intracranial manifestations is using contrast-enhanced magnetic resonance imaging (MRI). This technique shows low signal areas on T2-weighted images in the affected gyri and surrounding white matter, which may be caused by elevated deoxyhaemoglobin or calcification. Along with cortical atrophy and cerebral calcification, radiological studies also show tram-track calcifications on plain films, which are evident from about the age of one year.

Leptomeningeal enhancement may also be associated with choroid plexus enlargement and calcification on the afflicted side. An enlarged deep vein might be seen on an MRI or CT scan as a result of thrombosis or delayed flow in the superficial venous system. A bigger hemicranium or hemiatrophy may be the cause of cranial asymmetry, which is occasionally associated with subdural collections.

**Conclusion**

Phakomatoses group includes nearly 30 and more individual syndromes. Although genetic testing is available, manifestations of these syndromes cover a wide range. Imaging plays an important role in screening, early identification of abnormalities, and follow up of lesions in previously diagnosed cases. (13) Radiologists should be familiar with these syndromes to guide appropriate treatments and prognosis.

MRI is crucial for diagnosis, often revealing previously unnoticed lesions and contributing to a better understanding of these complex disorders. The necessity for screening and long-term follow-up for patients with these syndromes remains unresolved. Currently, MRI is an accepted tool for monitoring. Genetic assessment and counselling are essential, potentially leading to screening for asymptomatic relatives.

**References**


1. Swarup MS, Gupta S, Singh S, Prakash A, Mehndiratta A, Garg A. Phakomatoses: A pictorial review. Indian J Radiol Imaging. 2020 Apr;30(02):195–205.
2. Purkait R, Samanta T, Thakur S, Dhar S. NEUROCUTANEOUS SYNDROME: A PROSPECTIVE STUDY. Indian J Dermatol. 2011;56(4):375–9.
3. Braffman BH, Bilaniuk LT, Zimmerman RA. MR of central nervous system neoplasia of the phakomatoses. Semin Roentgenol. 1990 Apr 1;25(2):198–217.
4. Pfahler V, Ertl-Wagner B. Phakomatoses. In: Barkhof F, Jäger HR, Thurnher MM, Rovira À, editors. Clinical Neuroradiology: The ESNR Textbook [Internet]. Cham: Springer International Publishing; 2019 [cited 2024 Jul 28]. p. 1677–703. Available from: https://doi.org/10.1007/978-3-319-68536-6_34
5. Neurofibromatosis from Head to Toe: What the Radiologist Needs to Know [Internet]. [cited 2024 Oct 3]. Available from: https://pubs.rsna.org/doi/epdf/10.1148/rg.210235
6. Legius E, Messiaen L, Wolkenstein P, Pancza P, Avery RA, Berman Y, et al. Revised diagnostic

criteria for neurofibromatosis type 1 and Legius syndrome: an international consensus recommendation. Genet Med Off J Am Coll Med Genet. 2021 Aug;23(8):1506–13.

7. Herron J, Darrah R, Quaghebeur G. Intra-Cranial Manifestations of the Neurocutaneous Syndromes. Clin Radiol. 2000 Feb;55(2):82–98.
8. Smith MJ, Bowers NL, Bulman M, Gokhale C, Wallace AJ, King AT, et al. Revisiting neurofibromatosis type 2 diagnostic criteria to exclude LZTR1-related schwannomatosis. Neurology. 2017 Jan 3;88(1):87–92.
9. Lesions of skin and brain: modern imaging of the neurocutaneous syndromes. [Internet]. [cited 2024 Oct 3]. Available from: https://ajronline.org/doi/epdf/10.2214/ajr.158.6.1590106
10. Binderup ML, Galanakis M, Budtz-Jørgensen E, Kosteljanetz M, Bisgaard M. Prevalence, birth incidence, and penetrance of von Hippel–Lindau disease (vHL) in Denmark. Eur J Hum Genet. 2016 Dec 1;25.
11. Osborn's Brain: 3rd edition | Anne G. Osborn | ISBN: 9780443109379 | Elsevier Asia Bookstore [Internet]. [cited 2024 Oct 3]. Available from: https://www.asia.elsevierhealth.com/osborns-brain-9780443109379.html
12. Ruggieri M, Polizzi A, Marceca GP, Catanzaro S, Praticò AD, Di Rocco C. Introduction to phacomatoses (neurocutaneous disorders) in childhood. Childs Nerv Syst. 2020 Oct;36(10):2229–68.
13. Shin JH, Lee HK, Khang SK, Kim DW, Jeong AK, Ahn KJ, et al. Neuronal Tumors of the Central Nervous System: Radiologic Findings and Pathologic Correlation. RadioGraphics. 2002 Sep;22(5):1177–89.