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NEUROIMAGING FEATURES OF PHAKOMATOSES: CASE REPORTS AND A COMPREHENSIVE REVIEW

Radio-Diagnosis

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ABSTRACT

The neurocutaneous syndromes or phakomatoses are a heterogenous group of both congenital and acquired disorders manifesting with central nervous system and cutaneous abnormalities. These disorders predominantly affects the structures that are of ectodermal origin i.e skin, nervous system, and eyes which can have variable clinical presentation. The four most common phakomatoses or neurocutaneous disorders are neurofibromatosis (type 1 and 2), Sturge-Weber syndrome, tuberous sclerosis complex and von Hippel-Lindau disease. Imaging of the brain and spine plays an important role in the diagnosis and plan of management. We present five case reports of neurocutaneous syndrome presented to our department.

KEYWORDS

Tuberous sclerosis, Sturge-Weber syndrome, Von- Hippel Lindau syndrome, neurofibromatosis.

INTRODUCTION-

The neurocutaneous syndromes or phakomatoses are a heterogeneous group of disorders which primarily affects the structures that arise from the embryonic ectoderm. These syndromes typically affect the central nervous system, peripheral nerves, skin, connective tissue, and other organ systems. Classically, four diseases are included in this group, neurofibromatosis (type 1& type 2), tuberous sclerosis, and von Hippel-Lindau disease.

The genetic mutation has been identified in most of these entities which gives better understanding of the underlying pathophysiology through a tumor suppressor mechanism as well as a more precise confirmatory test and potentially a means of prenatal diagnosis[1]. Imaging plays an important role in the diagnosis by early identification, screening of family members and monitoring of affected individuals.

The imaging techniques include magnetic resonance imaging for CNS manifestations. Computed tomography and ultrasonography are useful for demonstrating abdominal manifestations. We present 5 case reports of neurocutaneous syndromes presented to our department.

Case reports

Case 1-

- A 20-year-old female patient reported to the department of radio diagnosis with a chief complaints of childhood onset epilepsy. History revealed that the reddish discoloration (port wine stain) was present on the right side of the face since birth and was gradually darkening with age.
- She was oldest of the three siblings born after full term by normal delivery. Family history was noncontributory. There was no visible sign of mental retardation and patient had no history of convulsions.
- Physical examination revealed a diffuse, flat reddish-purple patch on the right side of the face extending from the midline of the forehead, reaching superiorly up to the hairline, inferiorly down to the upper border of angle of mouth, laterally up to the left ear.
- Further she was referred for CEMRI brain, which revealed moderate atrophy of right cerebral hemisphere more so involving the parietal and occipital lobes with florid blooming along the gyri of right parieto-occipital region showing leptomeningeal enhancement in the overlying sulci with enlarged right choroid plexus and multiple abnormal venous channels in the right temporo-parieto-occipital region.
- With the afore mentioned clinical and radiological findings, a diagnosis of Sturge- weber syndrome was considered.

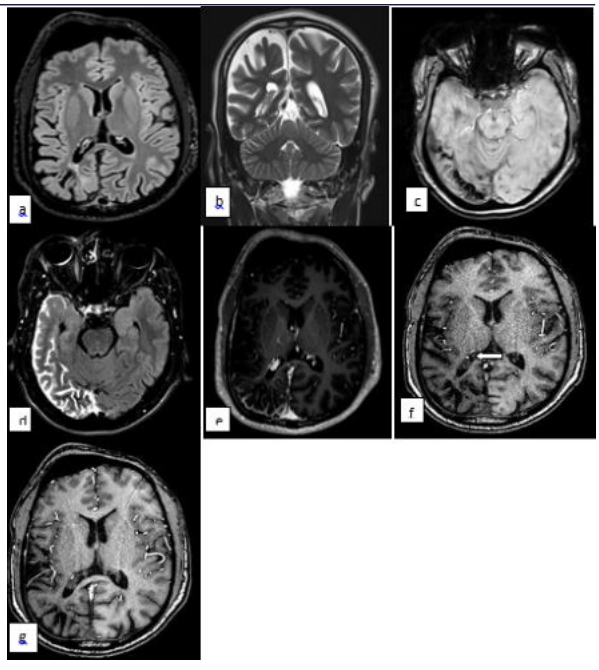


Fig 1- Axial FLAIR and coronal T2WI of MRI brain plain (a &b) showing moderate atrophy of the right cerebral hemisphere involving more of parietal and occipital lobes with enlarged right choroid plexus and enlargement of ipsilateral frontal sinus.

- Axial SWI images of plain MRI brain (c) showing serpentine areas of blooming along the gyri of right parieto-occipital lobes.
- Axial T1W post contrast images of MRI brain (d & e) showing leptomeningeal enhancement in the overlying sulci of right parieto-occipital lobe.
- Axial 3D TOF images (f) showing a prominent medullary vein extending along the pial sulcal space draining into choroid plexus. Fig (g) shows multiple abnormal venous channels in the right parieto-occipital region.

Case 2

- A 18 year old male presented with multiple skin lesions (angiofibromas) since 5 years and h/o epilepsy since the age of 10 and is on anticonvulsant treatment. He also gives history of

difficulty in understanding. He was born after full term by normal vaginal delivery and post-natal period was uneventful. He is the second child among three siblings and all are healthy. Past history and family history were insignificant.

- On general physical examination- few well-defined, brown nodular growths were seen on the forehead, cheeks, front and back trunk region-angiofibromas. A well-defined hypermelanotic patch was seen in the left lumbosacral region- suggestive of shagreen patch. Vital signs were found to be within normal limits.
- He was referred to department of Radio diagnosis with provisional clinical diagnosis of tuberous sclerosis.
- Further CEMRI brain was done which revealed multiple subependymal calcified nodules, few cortical and sub cortical areas of FLAIR hyper intensities suggesting cortical and sub cortical tubers. Small subependymal giant cell astrocytomas was seen at foramen of Monro.
- With the above mentioned clinical and radiological findings, diagnosis of tuberous sclerosis was considered.

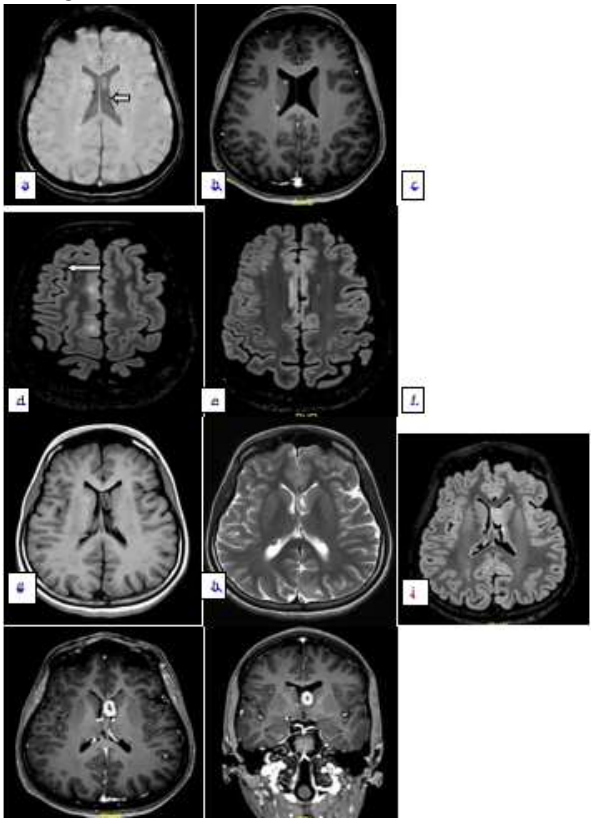


Fig 3- Axial SWI images of MRI brain plain (a) showing multiple small well defined bilateral calcified subependymal nodules, few of them showing enhancement (b)on post contrast images.

- Axial 3D FLAIR images (c & d) showing multiple cortical/ subcortical tubers.
- Axial MRI brain plain T1 and T2 W images (e & f) showing Subependymal giant cell astrocytoma in the region of foramen of Monro.
- Axial and coronal T1W post contrast MRI brain images (h & i) showing peripheral homogenous enhancement of the SEGA with central non enhancing area**.**

Case 3-

- The 42-year-old female presented with 3-month history of severe headache associated with giddiness. She also complaints of blood in urine since 2 weeks. No significant family history was present.
- Neurological examination showed the power of 4/5 in lower limbs. Rest of the systemic exanimation was normal. Her vitals were normal and initial laboratory investigations confirmed the presence of hematuria.
- Further she was referred to department of Radio diagnosis for CEMRI brain which showed a well defined intra-axial infratentorial cystic lesion with enhancing solid mural component in the right cerebellar hemisphere causing mass effects on the brain stem and 4th ventricle- possiblity of hemangioblastoma was considered.
- Further CEMRI spine was done which showed well defined heterointense intramedullary lesion with enhancing solid component in the dorsal spinal cord– s/o hemangioblastoma.
- CECT abdomen was done - which revealed multiple well defined heterogenously enhancing hyperdense mass lesion in bilateral kidneys- possibility of renal cell carcinoma was considered and it also showed multiple bilateral renal cysts and pancreatic cysts.
- Surgical removal of the renal mass lesion was done and HPE showed renal cell carcinoma.
- With the aforementioned clinical, radiological and pathological findings, a diagnosis of Von Hippel- Lindau disease was established.

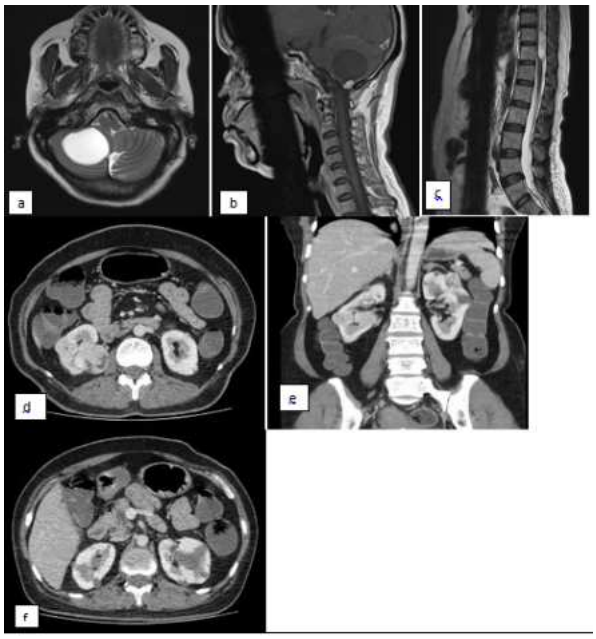


Fig 5 - Axial T2W plain MR image of brain (a) showing a well defined hyperintense cystic lesion in the right cerebellar hemisphere causing mass effects on brain stem and 4th ventricle. Axial T1 sagittal post contrast images (b) showing enhancing solid mural nodule of the lesion- s/o

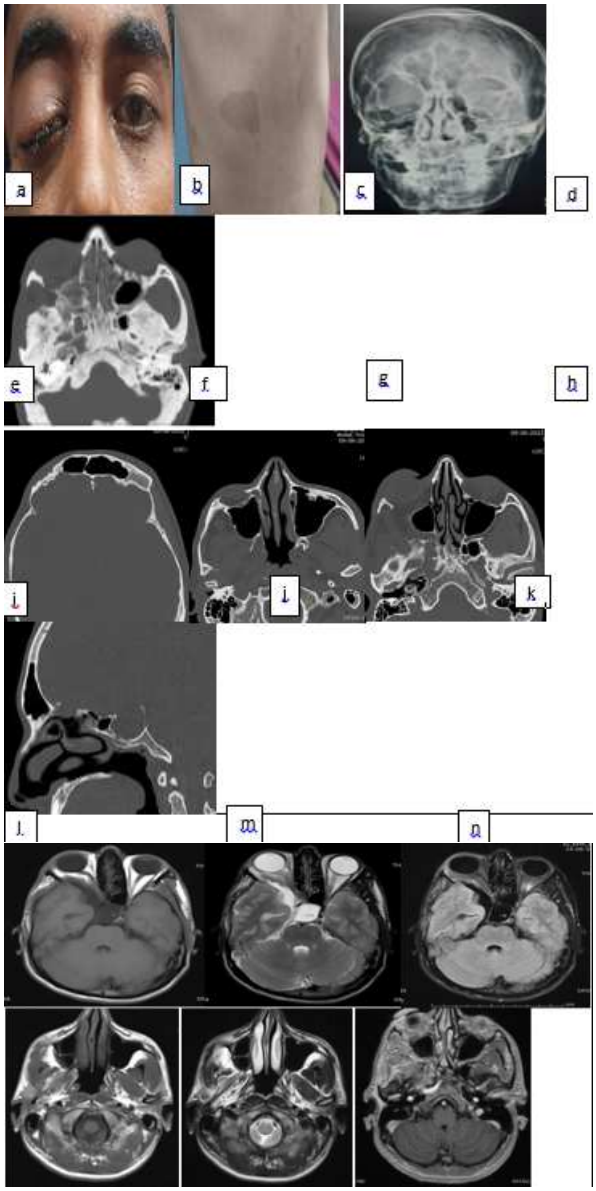
- hemangioblastoma.
- Sagittal T2 dorso-lumbar spine plain MR images (c) showing spinal hemangioblastoma in the dorsal spinal cord with syrinx and extensive perilesional spinal cord edema.
- Axial and coronal CECT abdomen images (d & e) showing multiple well defined heterogenously enhancing renal cell carcinoma in bilateral kidneys.
- Axial CECT images of the abdomen (f) showing multiple well defined bilateral simple renal cysts.

Case 4

- A 20 years old male presented with complaints of drooping of right eyelid since child hood with pain less anterior protrusion of right eye since child hood. No h/o decreased visual acuity. No significant family history noted.
- On general physical examination his vitals were stable, multiple café-au-lait spots with diameter > 1.5 cm were noted in the trunck and both extremities. Axillary and inguinal freckling was also seen.
- On ocular examination- There was ptosis of right eyelid with marked proptosis and globe enlargement of the right eye as compared to left. Lisch's nodules were seen on the iris in both the eyes.
- Further with a provisional diagnosis of Neurofibromatosis type 1, patient was referred to department of Radio diagnosis for CNS imaging.
- Preliminary Skull radiograph, PA view was obtained which showed a bare and large orbit on the right side, with dysplasia of the greater wing of the right sphenoid bone with normal lesser and greater wings of the sphenoid on the left side- giving bare orbit sign.
- Further NCCT brain was done which showed dysplastic right

greater wing of sphenoid bone with anterior bowing of right lesser wing of sphenoid bone, balloning of sella, solid periosteal reaction in right frontal bone and thinning of right zygomatic arch, squamous part of right temporal bone, condylar and coronoid process of right hemi mandible.

- Further CEMRI brain was done which showed an ill defined soft tissue thickening in right anterior temporal fossa associated with herniation of right anterior temporal lobe into the right orbit through defect in right sphenoid wing displacing right lateral rectus and optic nerve medially. Right temporalis, masseter, medial and lateral pterygoid muscles appears bulky, edematous with fatty infiltration showing heterogeneous enhancement on post contrast study.
- Widening of CSF space noted along the right anterior and medial aspect of right temporal convexity.
- With the afore mentioned clinical and radiological findings, a diagnosis of Neurofibromatosis type 1 was considered.



Case 5

- A 32 year old female patient presented with c/o sudden onset of slurring of speech since 1 day. She had a history of frequent on and off severe headache since 5 months. No h/o of seizures, weakness of U/L or L/L or blurring of vision. She also had complaints of severe non-radiating lower back pain since 5 months which increases on bending forward. She further gives history of Neurofibromatosis type 2 in her father.
- On general physical examination, vitals were stable. Neurological examination revealed decreased power of 4/5 in bilateral lower limbs. Rest of the systemic exanimation was normal.
- She was referred to department of Radio diagnosis for initial CT brain and MRI DL spine.
- Initial CT brain revealed a well defined extra axial, supratentorial, broad dural based hyperdense left frontal mass with central hyperdense calcification likely arising from the anterior clinoid process of sphenoid bone causing mass effects on the adjacent brain parenchyma- possibility of meningioma was considered.
- Further CEMRI brain revealed a well defined extra axial, supratentorial, broad dural based left frontal mass lesion with central calcification likely arising from the anterior clinoid process of sphenoid bone causing mass effects and showing dural tail and CSF cleft sign on post contrast images- possibility of meningioma was considered.
- Further CEMRI DL spine was done for severe back pain which showed a well defined vertically ovoid heterointense enhancing solid-cystic intradural extramedullary lesion in the left postero-lateral aspect of dorsal spinal canal causing compression and displacement of spinal cord to right and adjacent perineural enhancement of exiting nerve roots of D10- neoplastic etiology- possibility of nerve sheath tumor- schwannoma was considered.
- Further resection of spinal mass was done& HPE revealed Schwannoma.
- With the above mentioned clinical, radiological and histopathological findings Neurofibromatosis type 2 was established.

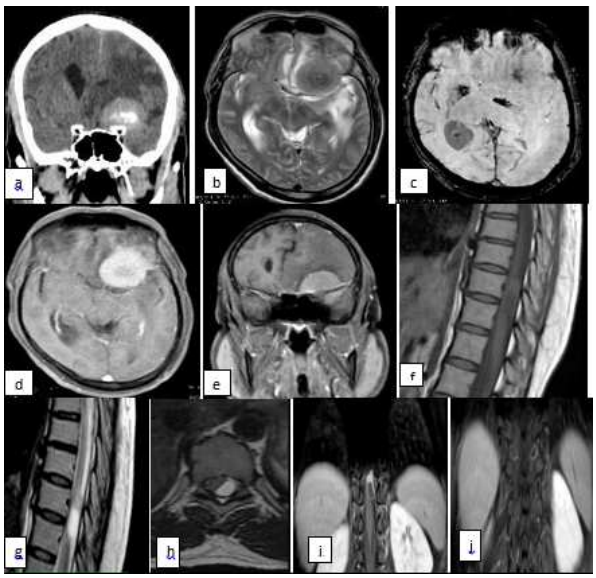


Fig 5- Coronal reformatted CT brain images (a) showing meningioma likely arising from left anterior clinoid process of sphenoid bone.

- Axial plain and contrast MRI brain T2WI (b to e) showing meningioma causing white matter edema and mass effects.
- Sagittal T1 & T2 W and axial 3D T2 W MRI DL spine plain and contrast images (f to i) showing schwannoma with adjacent perineural enhancement of exiting nerve roots (j).

DISCUSSION:

The neurocutaneous syndromes or phakomatoses are a heterogeneous group of disorders involving the central nervous system, peripheral nerves, skin, connective tissue and other organ systems. These disorders mainly involve structures of ectodermal origin. These syndromes typically affect the central nervous system (CNS). The four common neurocutaneous syndromes include neurofibromatosis (type 1 &2), Sturge-Weber disease, tuberous sclerosis and von Hippel-Lindau syndrome. Although these neurocutaneous syndromes are diagnosed clinically by a number of disease features, a spectrum of disease manifestation and severity in each of these syndromes sometimes makes the diagnosis challenging[1].

Imaging plays an important role in the early diagnosis, screening of family members and follow up of patients. The imaging technique of neurocutaneous syndromes includes magnetic resonance imaging, computed tomography and ultrasonography. Neuroimaging plays an important role in the clinical evaluation by identifying CNS lesions. It is also helpful in the initial diagnosis, in knowing the extent of the central nervous system involvement, in monitoring disease progression, and in surgical management.

1) Sturge Weber syndrome

Sturge-Weber syndrome also called as encephalotrigeminal angiomatosis is characterized by congenital hamartomatous malformations which may affect the skin, eye and central nervous system, characterized by formation of angiomas involving the face, choroid and leptomeninges. It is the third most common neurocutaneous syndrome after neurofibromatosis and tuberous sclerosis.[5]. The incidence of Sturge-Weber syndrome is estimated to be 1 in 20,000-50,000 live births[7].

Sturge-Weber syndrome is caused by somatic mosaic mutations in the GNAQ gene which is located on the long arm of chromosome 9[6]. The neurologic manifestations of SWS include atonic, tonic, or myoclonic seizures.

Diagnosis of Sturge-Weber syndrome is based on typical clinical symptoms, facial appearance, and brain magnetic resonance imaging (MRI) findings. On skull radiographs, gyriform calcifications can be seen and are classically described as 'tram-track sign' or 'railroad-track sign'. CT is the best modality for detecting calcifications and other changes such as cortical atrophy and leptomeningeal enhancement on the post-contrast studies. In the early phase, on MRI there will be leptomeningeal enhancement along the sulci. In the late phase, T2 hyperintensity seen in the region of gliosis with decreased pial enhancement and cortical atrophy with enlarged choroid plexus with lack of superficial cortical veins with prominent deep medullary/subependymal veins.

2) Neurofibromatosis

Neurofibromatosis type 1 (NF1) and neurofibromatosis type 2 (NF2) are autosomal dominant inherited neurocutaneous disorders with a wide range of clinical and imaging manifestations. NF1, also known as von Recklinghausen disease and is the most common phakomatoses with clinical manifestations including café-au-lait macules, neurofibromas or plexiform neurofibromas, axillary or inguinal freckling, optic pathway gliomas, Lisch nodules and osseous lesions such as sphenoid dysplasia and other manifestations such as low-grade gliomas, interstitial lung disease, various abdomino-pelvic neoplasms, scoliosis, and vascular dysplasias can also be seen. Classic manifestations of NF2 include schwannomas, meningiomas, and ependymomas[2].

a) Neurofibromatosis Type 1

NF1 has a prevalence of at least one in 4000–5000[3] occurring due to loss-of-function mutations in the tumor suppressor gene *NF1*, located at chromosome 17q11.2 [4]. Clinical manifestations in NF1 patients can vary significantly where they can appear in infancy or early childhood. Central Nervous System Manifestations of NF 1 include focal areas of signal intensity (FASI's), Optic pathway gliomas, non–optic pathway intracranial gliomas, dural ectasia and meningocele, neurofibromas and plexiform neurofibromas and malignant peripheral nerve sheath tumors.

b) Neurofibromatosis Type 2

NF2 has a prevalence of one in 60 000[3] due to loss-of-function mutations in the *NF2* gene located at chromosome 22q11.2. Central Nervous System Manifestations of NF 2include schwannomas, intracranial and spinal meningiomas and ependymomas.

3) Tuberous sclerosis

Tuberous sclerosis is a rare genetic autosomal-dominant disorder with a prevalence from one in 6,000 to one in 12,000[8]. It is a multisystem disorder affecting the lungs, skin, kidneys as well as brain resulting in conditions like autism, epilepsy, and intellectual disability. The mutations on either of the two genes, TSC1 and TSC2, which encode for the proteins hamartin and tuberin, respectively are the causes of Tuberous sclerosis. This leads to the growth of hamartomas in various organs, such as cortical tubers, subependymal nodules and subependymal giant cell astrocytomas in brain, renal angiomyolipomas, lymphangioleiomyomatosis in lungs, cardiac rhabdomyomas and angiofibroma, Shagreen patch and hypomelanotic macule in skin[8].Tuberous typically shows three clinical features consisting of mental retardation, epilepsy, and facial angiofibroma which constitutes the Vogt triad.

The intracranial manifestations of tuberous sclerosis include cortical or subcortical tubers, subependymal nodules, subependymal giant cell astrocytomas and white matter heterotopias.

4) Von Hippel-Lindau disease

Von Hippel-Lindau syndrome is an autosomal dominant syndrome with a prevalence of around one in 36 000 and one in 50 000 live births [11] which is characterized by various benign and malignant tumors in multiple organs most commonly includes hemangioblastoma (cerebellar, retinal and spinal), pheochromocytoma, renal cell carcinoma and pancreatic tumors, as well as cysts in multiple organs.

VHL is a tumor suppressor gene which is located on chromosome 3p25–26 that plays an important role in the hydroxylation of the hypoxia-inducible factor 1 alpha (HIF-a) under normoxic conditions. In VHL, the VHL gene becomes non-functional[11].

The clinical diagnosis of VHL can be made in the following circumstances[11]: (a) in a patient with a family history of VHL and at least one of the characteristic VHL-related tumors (eg, retinal HBs, CNS HBs, clear cell RCCs, pancreatic NETs, and endolymphatic sac tumors); (b) in the presence of two or more retinal or CNS HBs; or (c) in the presence of one retinal or CNS HB, plus at least one of the characteristic VHL-related visceral tumors, excluding renal and epididymal cysts.

CONCLUSION:

The phakomatoses are a group of disorders that affects the structures that arise from the embryonic ectoderm. These include four diseases in this group, neurofibromatosis (type 1& type 2), tuberous sclerosis, and von Hippel-Lindau disease. Although genetic testing is available, there is wide range of manifestations that cover this syndrome. Imaging plays an important role in the screening of family members, early diagnosis and follow-up of lesions. Radiologists should be familiar with these syndromes to guide appropriate treatment and prognosis. Hence, early diagnosis is important along with the regular surveillance, so that early management can be done to prevent complications.

REFERENCES:

1) Lin DDM, Barker PB. Neuroimaging of Phakomatoses. Seminars in Pediatric Neurology. 2006 Mar;13(1):48–62.
2) Wang MX, Dillman JR, Guccione J, Habiba A, Maher M, Kamel S, et al. Neurofibromatosis from Head to Toe: What the Radiologist Needs to Know. RadioGraphics. 2022 Jul;42(4):1123–44.
3) Ferner RE. The neurofibromatoses. Practical Neurology. 2010 Mar 22;10(2):82–93.
4) Jouhilahti EM, Peltonen S, Heape AM, Peltonen J. The Pathoetiology of Neurofibromatosis 1. The American Journal of Pathology. 2011 May;178(5):1932–9.
5) Comi A. Current Therapeutic Options in Sturge-Weber Syndrome. Seminars in Pediatric Neurology. 2015 Dec;22(4):295–301.
6) Shirley MD, Tang H, Gallione CJ, Baugher JD, Frelin LP, Cohen B, et al. Sturge–Weber Syndrome and Port-Wine Stains Caused by Somatic Mutation in GNAQ. The New England journal of medicine [Internet]. 2013 May 23;368(21):1971–9. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3749068/
7) Singh AK, Keenaghan M. Sturge-Weber Syndrome. 2023 May 1. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan–. PMID: 29083797.
8) Dzefi-Tettey K, Edzie EK, Gorleku P, Piersson AD, Cudjoe O. Tuberous Sclerosis: A Case Report and Review of the Literature. Cureus. 2021 Jan 4;
9) Kalantari BN, Salamon N. Neuroimaging of Tuberous Sclerosis: Spectrum of Pathologic Findings and Frontiers in Imaging. American Journal of Roentgenology. 2008 May 1;190(5):W304–9.
10) Wang MX, Segaran N, Bhalla S, Pickhardt PJ, Lubner MG, Katabathina VS, et al. Tuberous Sclerosis: Current Update. RadioGraphics. 2021 Nov;41(7):1992–2010.
11) Ganeshan, D. et al. (2018) 'Tumors in von hippel–lindau syndrome: From head to toe—comprehensive state-of-the-art review', RadioGraphics, 38(3), pp. 982–982. doi:10.1148/rg.2018184005.
12) Wong WT, Agrón E, Coleman HR, et al. Clinical characterization of retinal capillary hemangioblastomas in a large population of patients with von Hippel-Lindau disease. Ophthalmology 2008;115(1):181–188.
13) Leung RS, Biswas SV, Duncan M, Rankin S. Imaging Features of von Hippel–Lindau Disease. RadioGraphics. 2008 Jan;28(1):65–79.