NEUROIMAGING IN PEDIATRIC PHAKOMATOSES.  
AN EDUCATIONAL REVIEW  
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Abstract  
Phakomatoses are a group of more than 30 entities with an inheritance pattern that primarily affects the central nervous system, skin, viscera and connective tissue. The aim of this paper is to make an educational review of the most common radiological findings on phakomatoses through the iconography of the cases collected in our magnetic resonance imaging (MRI) and computer tomography (CT) units over the last ten years. Also, we describe and illustrate by these techniques the main features of the most common entities within the wide spectrum of diseases. As highly variable and age dependent, imaging techniques have an important role in the diagnosis and follow-up of these patients. Increased awareness for the need to implement and conduct screening programs could be considered as a solution to prevent late diagnosis and to treat the patients in early stages of disease.  

Keywords: phakomatoses, white matter diseases, magnetic resonance imaging, computer tomography, neurofibromatosis  

Introduction  
The term “Phakomatoses” (after the word “phakos”, meaning birthmark) was formulated by the ophthalmologist Van der Hoeve in the 20th century when he described the retinal hamartomas [1]. Phakomatoses or neurocutaneous syndromes are a heterogeneous group of congenital disorders with variable degree of penetration, primarily involving structures derived from the embryological neuroectoderm. All those syndromes involve the central nervous system and the peripheral nerves in common; the skin, eye and other systems may also be involved [2].  
The main phakomatoses include neurofibromatosis type 1 (NF1), neurofibromatosis type 2 (NF2), tuberous sclerosis complex (TSC), Von Hippel-Lindau (VHL) syndrome and Sturge-Weber syndrome (SWS). But the group of phakomatoses is larger (more than 30 entities) and primarily affect the central nervous system, and less the skin, viscera and connective tissue. There are exceptions to this rule, so there is no skin involvement in VHL syndrome and Type 3 of SWS.  

Neuroimaging has an important role in this pathology for several reasons [3]. The most important role is its diagnostic use, due to the pathognomonic appearance that may be presented by some cases and because it may confirm a clinical suspicion of an unexpected event. Also, neuroimaging is important to rule out family involvement and to organize regular monitoring.  

In this paper, our aim is to present the most representative images of the cases we have collected. The technique of choice is magnetic resonance imaging (MRI) for the study of central nervous system, with the contribution of other techniques such as computer tomography (CT) especially for the study of the pathology of pediatric patient.  

Epidemiology  
For NF1 the prevalence was 1-5/10 000 in France
NF2, TSC, SWS and VHL have the same prevalence of 1-9/100,000 in France and an incidence of 1/40,000 for NF2, 1/20,000 for TSC and 1/50,000 for SWS and VHL syndrome in USA according to OMS [6].

**General Pathogenesis**

Phakomatoses are a heterogeneous group with an inheritance pattern and variable expression [2], corresponding in some cases to a new, spontaneous mutation, while in other cases to congenital malformations, hence the importance of performing genetic counseling and genetic testing [3]. The defect is related to a tumor suppression gene (Table I). They are all autosomal dominant disorders with high penetration (in some cases 100% penetrance) [6]. Although all are inherited dominant neurocutaneous disorders, they are clinically, genetically and radiologically distinct diseases and should be considered as separated entities.

**Table I.** The involved chromosome and encoded protein for each phakomatosis.

| Disease name | Chromosome |
|--------------|------------|
| NF1          | 17q        | Neurofibromin |
| NF2          | 22q        | Merlin        |
| TSC1         | 9q         | Hamartin      |
| TSC2         | 16p        | Tuberin       |
| VHL          | 3p         | Cell cycle regulation |

**Neurofibromatosis type I (NF1)**

**I. Pathology**

Also named Von Recklinghausen disease, type I neurofibromatosis is known as classical or peripheral phakomatosis, characterized by the involvement of the nerve sheath [2]. Oligodendrocyte myelin glycoprotein and neurofibromin is embedded in gene. This may be responsible for the dysplasia of the white matter lesions in the brain [6].

**II. Clinical issues**

The most common clinical presentation is with café-au-lait spots (the earliest sign) and learning disabilities. Two or more criteria must be present for a diagnosis of NF1 (Table II). As shown in table II clinical and neuroimaging (*) findings are included in the diagnostic criteria for NF1 [2].

**III. Imaging findings:** White matter (WM) lesions may also involve dentate nuclei of cerebellum, globus pallidus, thalamus, brainstem, pons, midbrain, hippocampus [7]. Bone lesions are associated with plexiform neurofibromas. For example scalp lesions which are over the occiput, skull base lesions extending into retropharynx or orbital lesions extending from cavernous sinus through orbit into periorbital soft tissues [6]. The plexiform neurofibromas appear as irregular, cylindrical, fusiform or nodular ill-defined thickening of the major nerve trunks [8]. Visual pathway gliomas can be found at the level of intra-orbital optic nerves (ONG), chiasm/hypothalamus, optic tracts, lateral geniculate bodies and radiations (Tables III, IV).

**Table II.** Criteria for the diagnosis of NF1.

| Criteria | Postpuberal (≥ 1.5 cm) | Prepuberal (≥ 0.5 cm) |
|----------|------------------------|----------------------|
| 1 Five or more café-au-lait spots | 1.5 cm or larger | 0.5 cm or larger |
| 2 Two or more neurofibromas | 1.5 cm or larger | 0.5 cm or larger |
| 3 Axillary/inguinal freckling | -benign iris hamartomas |
| 4 Visual pathway glioma (*) | -dysplasia of the sphenoid bone |
| 5 Two or more Lisch nodules | -dysplasia or thinning of long bone |
| 6 A distinctive bony lesion (*) | |
| 7 First degree relative with NF1 | |

**Neurofibromatosis type II (NF2)**

**I. Pathology**

NF2 is a hereditary syndrome characterized by multiple cranial nerve schwannomas, meningiomas and spinal tumors (Table V and VI). It has been considered synonym with “bilateral acoustic schwannomas”[2].

**II. Clinical issues**

The most common signs and symptoms are: hearing loss, vertigo, cranial neuropathies, scoliosis, paraplegia or neck pain [2]. Generally there are young patients becoming symptomatic in 3rd decade with multiple cranial neuropathies, cataracts and extremity weakness.

The diagnostic criteria for NF2 are:

- Bilateral vestibular schwannomas or
- 1st degree relative with NF2 and either a vestibular schwannoma or two of the following: neurofibroma, meningioma, glioma, schwannoma, juvenile posterior subcapsular lenticular opacity (cataract) [9].

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Table III. CT findings in NF1 (*CTA- computer tomography angiography, NECT- non-contrast enhanced CT, CECT- contrast enhanced CT).

| CT Findings |
|-------------|
| *CTA Vascular dysplasia - moyamoya, aneurysm |
| Sphenoid dysplasia, associated enlargement of middle cranial fossa and ipsilateral proptosis; enlargement optic nerves and chiasm |
| CECT Enhancing visual pathway gliomas |

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MRI Findings

- **T1**: WM lesions have variable signal – irregular hyperintensity may reflect myelin clumping or microcalcification.
- **T2**: Focal areas of signal intensity (FASI) – Image 1- are hyperintense and typically poorly defined. T2 may be more sensitive than FLAIR for WM lesions in cerebellum. ONG are isointense/hyperintense to normal brain.
- **STIR**: Excellent definition of plexiform and paraspinal neurofibromas.
- **T1 C+ FS**: Best sequence for evaluation of visual pathway gliomas.
- **MRA**: Valuable in detection of moyamoya and aneurysms.
- **MRS**: May have benefit in evaluation of WM lesions to distinguish from visual pathway glioma (WM lesions have relative preservation of NAA/glioma have ↓NAA with choline).

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|--------------|
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**III. Imaging**

**Table IV. MRI findings in NF1** (*STIR*- short T1 inversion recovery, T1 C+ FS- T1 contrast enhanced T1 with fat suppression, FLAIR – fluid attenuated inversion recovery, MRA- MR angiography, MRS- MR spectroscopy NAA-N-acetylaspartate).

**CT Findings**

- **NECT**: Vestibular schwannoma - cerebellopontine angle (CPA) mass, widened internal auditory canal (IAC), isodense/hyperdense. Meningioma – high density dural-based mass. Non-neoplastic cerebral calcification (extensive choroid plexus, cortical surface, ventricular lining).
- **CECT**: Cranial nerve tumor enhancement, meningioma enhancement.

**III. Imaging**

**Table V. CT findings in NF2.**

| CT Findings |
|-------------|
| **NECT**    | Vestibular schwannoma - cerebellopontine angle (CPA) mass, widened internal auditory canal (IAC), isodense/hyperdense. Meningioma – high density dural-based mass. Non-neoplastic cerebral calcification (extensive choroid plexus, cortical surface, ventricular lining). |
| **CECT**    | Cranial nerve tumor enhancement, meningioma enhancement. |

**Table VI. MRI findings in NF2** (T2* GRE- T2 gradient recalled echo, DWI- diffusion weighted imaging).

| MR Findings |
|-------------|
| **T1**      | Schwannomas – are hypointense to isointense, rare cystic change (Image 2). Meningiomas – isointense to hypointense, calcifications. |
| **T2**      | Schwannomas – small intracanalicular lesions can be shown on high resolution T2. |
| **T2*GRE**  | Shows nonneoplastic calcifications. |
| **DWI**     | Some meningiomas have restricted diffusion – characteristic of atypical or malignant meningioma. |
| **T1C+**    | Schwannomas – enhancement, usually homogeneous, with fat saturation and thin slice profile essential for small CN tumors. |
| **MRS**     | Meningioma – absent NAA peak, +/- lactate. Schwannoma – absent NAA peak, usually no lactate. |
Tuberous sclerosis complex (TSC)

I. Pathology
Also known as Bourneville disease, it is an autosomal dominant inherited neurocutaneous syndrome, characterized by the presence of hamartomas that behave as slow-growing painless masses with relatively normal cells in disorganized arrangement. In 60% of cases there is a spontaneous mutation in a tumor suppressor gene [9,10].

II. Clinical issues
The most common presentation is with the classic triad: skin lesion (facial angiofibromas), mental retardation and epileptic seizures [11,12]

Diagnostic criteria (Table VII) [13]:
- definite diagnosis: two major features or one major and two minor features
- probable diagnosis: one major feature plus one minor feature

The cortical tubers appear in 95% of patients (50% are cortical and subcortical in frontal lobe) [14]. They are parts of the outer layer of the brain that did not developed correctly and may present a characteristic appearance of an enlarged or misshapen gyrus, with a core of abnormal water signal instead of myelin-matching intensity. It can also calcify over years [13].

III. Imaging findings
The cortical/subcortical tubers (Image 3) are located mostly in frontal lobe, then parietal, occipital, temporal lobes and less in cerebellum. The best diagnostic tools are CT and MRI (Table VIII and IX).

At grey scale ultrasound rhabdomyomas are identifiable as early as 20 weeks gestation [9]. Cardiac rhabdomyomas and CNS tumors detected on fetal ultrasound represent a marker of tuberous sclerosis [15].

Table VII. Major and minor features of tuberous sclerosis complex.

| Major features                                      | Minor features                        |
|-----------------------------------------------------|---------------------------------------|
| Facial angiofibromas/forehead plaque                 | Multiple pits in dental enamel         |
| ≥3 hypomelanotic macules                            | Hamartomatous rectal polyps            |
| Cortical tubers                                     | Bone cysts                            |
| Subependymal nodules/astrocytomas                   | Cerebral WM radial migration lines     |
| Retinal hamartomas                                  | Multiple renal cysts                   |
| Lymphangioleiomyomatosis                            | Gingival fibromas                      |
| Renal angiomyolipomas                               | “Confetti” skin lesions                |
| Cardiac rhabdomyomas                                | Retinal achromatic patches             |
| Shagreen patches (connective tissue nevus)          |                                       |
| Sub/periungual fibromas                             |                                       |

Image 2.A: Axial T1 C+ shows bilateral enhancing vestibular schwannommas bulging from IAC into CPA cisterns in a patient with NF2 (cited from: http://www.massgeneral.org/cancer/news/newsarticle.aspx?id=2200).

Image 2.B: Coronal T1 C+ shows bilateral enhancing schwannomas of CN 5,6,8 and solitary meningioma into left CPA in a 31 year old man with multiple cranial neuropathies.
Sturge-Weber syndrome (SWS)

I. Pathology

Also known as angiomatosis encephalo-trigeminal, SWS has an uncertain origin, having raised the possibility of sporadic origin [16]. Most probably there is a somatic mutation or cutaneous mosaicism. At 4-8 weeks of gestation the embryonic cortical veins fail to coalesce and develop and is followed by deep venous occlusion with anoxic cortex [6]. The choroid plexus is commonly involved with an angiomatous change that includes both gross enlargement and increased vascularity [17].

II. Clinical issues

The intracranial leptomeningeal angiomatosis and bone marrow abnormalities is a key diagnostic feature in SWS [18]. Facial lesion are visible at birth and the seizures develop in the first year of life. The consequences of coroidal angioma is the increased intraocular pressure with buphthalmos [19]. It appear as atrophic cortex with dystrophic calcifications, with consequent widening adjacent subarachnoid spaces – “tram sign”. On the basis of the leptomeningeal malformation with consecutive cerebral calcification and progressive cerebrar atrophy, epilepsy is often at the forefront of the clinical findings [9].

Table VIII. CT findings in TSC.

| CT findings                      |
|----------------------------------|
| NECT Subependymal nodules (NsE-50% calcified by 10 years/along the lateral margins of the lateral ventricles) |
| Tubers – early: low density/ calcifications cortical/ subcortical mass |
| Later: isodense/calcifications |
| Ventriclemegalay common even without AsE |
| CECT Enhancing/enlarging NsE suspicious for AsE |

Table IX. MRI findings in TSC (*Cr-creatine).

| MR Findings                      |
|----------------------------------|
| T1 Cortical/subcortical tubers: early T1 increased, but variable after myelin maturation |
| T2/FLAIR Variable signal (relative to myelin maturation) |
| WM lesions – streaky linear or wedge-shaped hyperintensities (along radial migration lines from ventricle to cortex) |
| T2*GRE Calcified NsE more readily discerned |
| DWI Increased ADC values in epileptogenic tubers |
| T1C+ NsE enhancement more visible on MR than on CT (30-80% enhance- enlarging NsE at foramen of Monro: AsE) – Image 3 |
| 12% cortical/subependymal tubers enhance |
| MRS Low NAA/Cr, increased ml/Cr in subcortical tubers, NsE |

Image 3. Subependymal astrocytomas and cortical tubers in a 2 year old boy with seizures.

3.A/B (axial T2 ),C ( coronal T1 C+) show cortical/subcortical tubers expanding the gyri and calcified subependymal nodules in the lateral ventricules.
**III. Imaging findings**

The best diagnostic clue is cortical calcium [19], atrophy and enlarged ipsilateral choroid plexus (Tables X and XI). The pialangiomatosis is mostly unilateral (80% of cases) and the occipital lobes are much more affected than the parietal or frontoparietal ones.

**Table X.** CT findings in SWS.

| CT findings                        |
|-----------------------------------|
| NECT                              |
| Gyral/subcortical WM with calcium (Image 4B), progressive posterior to anterior |
| Late –atrophy, hyperpneumatization of paranasal sinuses, thick diploe            |
| CECT                              |
| Serpentine leptomeningeal enhancement                                      |

**Table XI.** MRI findings in SWS.

| MR findings                        |
|-----------------------------------|
| T1                                 |
| Increased WM volume subjacent to pial angiomatosis on early stage and atrophy of WM and GM on late stages |
| T2                                 |
| Early: transient hyperperfusion    |
| Late: increased signal in region of gliosis and low cortical signal in calcificated regions [19] |
| Late: Gliosis in involved lobes    |
| FLAIR                             |
| FLAIR T1+ improved visualization of enhancement                               |
| T2*GRE                            |
| Tram-track gyral calcifications   |
| DWI                               |
| Restricted diffusion in acute ischemia                                       |
| Early: serpentine leptomeningeal enhancement, pial angiomatosis of subarachnoid space (Image 4A) |
| T1C+                              |
| Engorged, enhancing choroid plexus                                          |
| MRS                               |
| Increased choline and low NAA in affected area                               |

**Image 4.** Left brain hemisphere with pial angiomatosis in a one-year-old child with infantile seizures.  
4.A (axial T1 C + MR) shows serpentine leptomeningeal enhancement of the left hemisphere and engorgement of the choroid plexus.  
4.B (axial Brain NECT) showing subcortical WM calcification in bilateral frontal lobes.

**Von Hippel Lindau syndrome (VHL)**

**I. Pathology**

Hereditary disease of autosomal dominant transmission with incomplete penetration and without skin involvement, unlike most phakomatoses [20]. The age of onset is variable, uncommon in children. It is characterized by the development of a variety of benign
and malignant tumors.

The most common causes of death in VHL disease patients are neurologic complications from cerebellar hemangioblastomas (HGBL) and renal cell carcinoma [21].

II. Clinical issues

The most common lesions are (Tables XII and ):

- Retinal angiomas → visual symptoms or vitreous hemorrhages
- HGBL of cerebellum and spinal cords → headache

| Table XII. CT findings in VHL. |
|-----------------------------|
| **CT findings** |
| NECT | HGBL in 70% of cases are well-delineated cerebellar cyst with nodule
| Cystadenoma of endolymphatic sac (ELS) produces destructive changes in petrous bone and intratumoral bone which is stippled, reticular or speculated |
| CECT | Intense enhancement of tumor nodule |

| Table XIII. MRI findings in VHL. |
|-----------------------------|
| **MR findings [6]** |
| T1 | HGBL: mixed iso to hypointense nodule +/- “flow voids” (large feeding vessels within the periphery or solid component may appear as tubular areas of flow void) [21]
| Associated cyst slightly hyperintense to cerebrospinal fluid |
| Cystadenoma of ELS: heterogeneous hyper/hypointense |
| T2/FLAIR | HGBL: hyperintense nodule, cyst |
| Cystadenoma of ELS: hyperintense mass |
| T2 | HGBL: blooms if hemorrhage is present (Image 5A) |
| T1C+ | HGBL: tumor nodule enhances strongly; cyst wall does not enhance (Image 5B)
| May detect tiny asymptomatic enhancing nodules |

- Visceral cysts and tumors (pheochromocytoma, renal cell carcinoma, pancreatic cysts or islet cell tumors, cystadenoma of endolymphatic sac [22])
- For the diagnosis of VHL disease the following lesions must be present:
  - capillary HGBL in central nervous system (CNS) or retina
  - one of typical VHL-associated tumors
  - previous family history [6]

III. Imaging findings

Image 5A. (axial T1 C+ ) shows hyperintense nodule into a peritumoral cyst in the cerebellum and

5B. ( axial T2 C+) shows a strongly enhancing solid tumor nodule in a patient with hemangioblastoma and family history of Von Hippel Lindau disease [23]
IV. Discussion and conclusion

Although genetic testing is available, the neurological manifestations of these syndromes cover a wide range, as described in this paper; therefore imaging plays an important key role in identification of abnormalities and follow-up of lesions.

Screening would be useful because some lesions in phakomatoses are treatable. Thus, early detection allows use of more conservative therapy and may improve the patient’s quality of life [21]. The best imaging tool is MRI.

For NF1, the evolution ranges from a progressive increase to regression. The best diagnostic clues are: hyperintense lesions on T2W1, plexiform neurofibromas and visual pathway gliomas. Referring to the size, WM lesions can measure 2-20 mm, visual pathway gliomas 3-50 mm and plexiform lesions can be massive [6].

For NF2 patients with vestibular schwannoma, enhancement is present on T1C+, usually homogeneous, with fat saturation and thin slice profile essential for small CN tumors.

In DWI some meningiomas have restricted diffusion which is mostly characteristic for atypical or malignant meningioma.

In Bourneville disease lesions of cerebellum developed subependymal giant cell astrocytoma in higher percentage than those without lesions of cerebellum [24]. The increased number of tubers increases the neurologic symptoms. WM lesions are along lines of neuronal migration and are cyst-like with the appearance of a cystoid brain degeneration. Thickened cortex and enlarged gyri may also be found. Sometimes these lesions regress spontaneously [6]. Oral rapamycin (sirolimus) therapy has shown promise in inducing regression of AsE and may be an alternative to surgical resection [10,25].

For SWS patients the prognosis is dismal if there are early onset seizures, refractory to medical treatment, extensive cortical atrophy and leptomeningeal angioma and if hemiparesis and cognitive deterioration occurs [26].

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