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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

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[4] and the incidence was 1/3000 in USA [5].

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	Encoded protein
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.

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

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
NECT	Sphenoid dysplasia, associated enlargement of middle cranial fossa and ipsilateral proptosis; enlargement optic nerves and chiasm
CECT	Enhancing visual pathway gliomas

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].

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).

	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↓

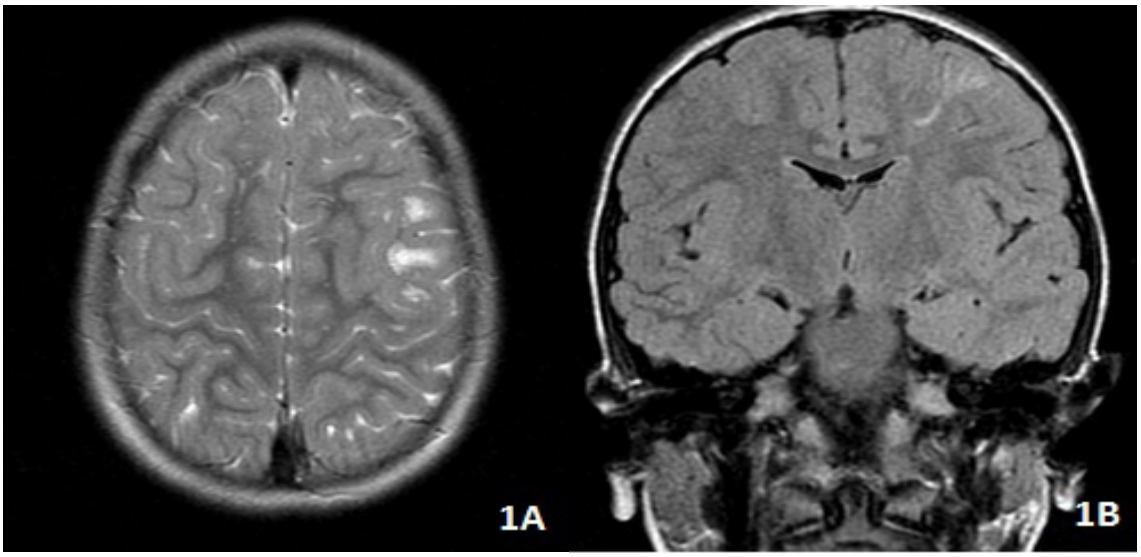

Image 1A axial T2) and **1B** (coronal Flair) show focal areas of increased signal intensity in subcortical white matter (FASI) of left parietal lobe in a 10 year old boy with short stature, multiple "café au lait" spots and learning disabilities.

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 nonneoplasic 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

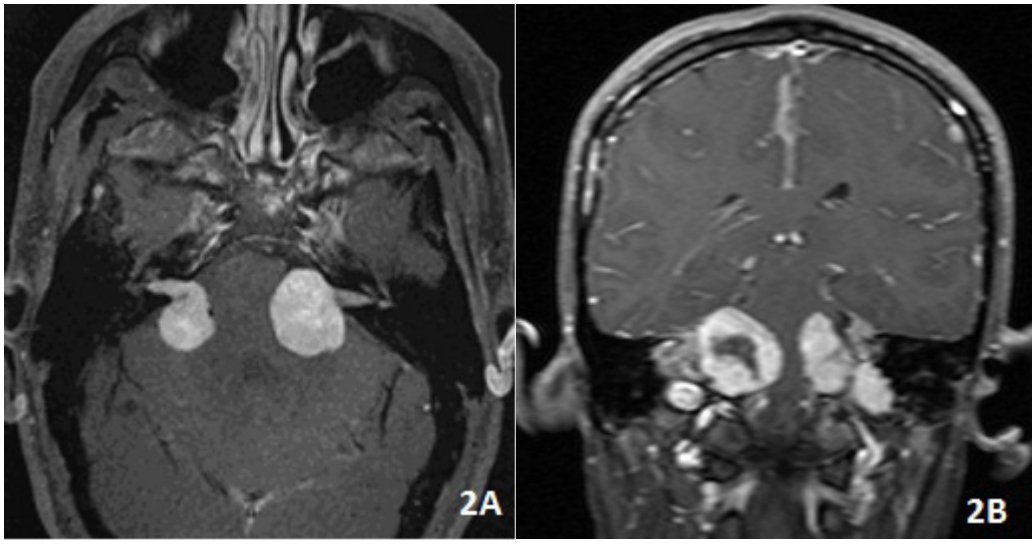

Image 2.A :Axial T1 C+ shows bilateral enhancing vestibular schwanommas bulging from IAC into CPA cisterns in a patient with NF2 (cited from: http://www.massgeneral.org/cancer/news/newsarticle.aspx?id=2200).
Image 2.B Coronal T1 C+ shows bilateral enhancing schwanomas of CN 5,6,8 and solitary meningioma into left CPA in a 31 year old man with multiple cranial neuropathies.

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 features

- possible diagnosis: one major feature OR two or more minor features

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	

Table VIII. CT findings in TSC.

	CT findings
NECT	Subependymal noduls (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
	Ventriculomegaly 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

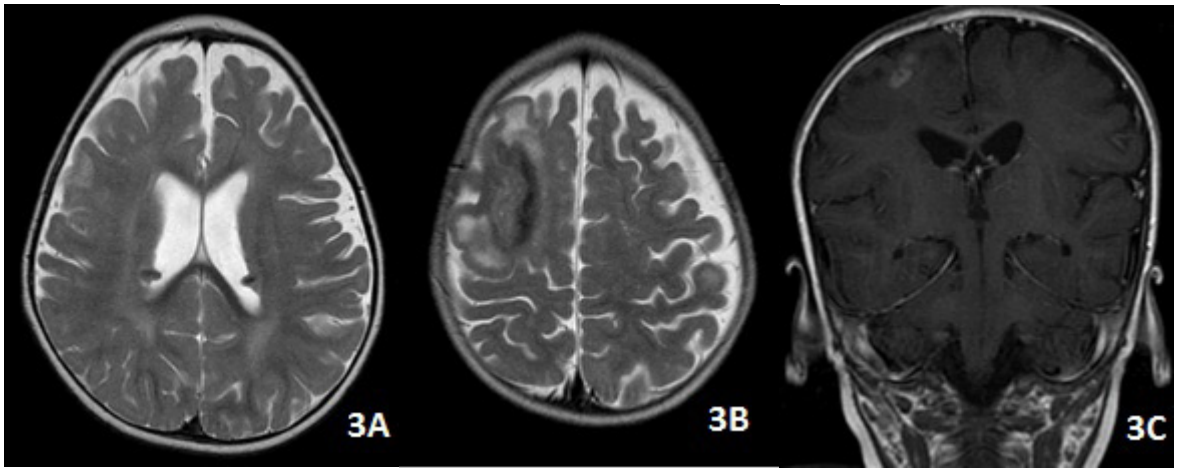

Image 3. Subependymal astrocytomas and cortical tubers in a 2 year old boy with seizures.
3.A/B (axial T2),C (coronal T1 C+) show cortical /subcortical tubers expanding the gyri and calcified subependymal nodules in the lateral ventricules.

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 cerebral atrophy, epilepsy is often at the forefront of the clinical findings [9].

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
DwWI	Restricted diffusion in acute ischemia
T1C+	Early: serpentine leptomeningeal enhancement, pial angiomatosis of subarachnoid space (Image 4A) Engorged, enhancing choroid plexus
MRS	Increased choline and low NAA in affected area

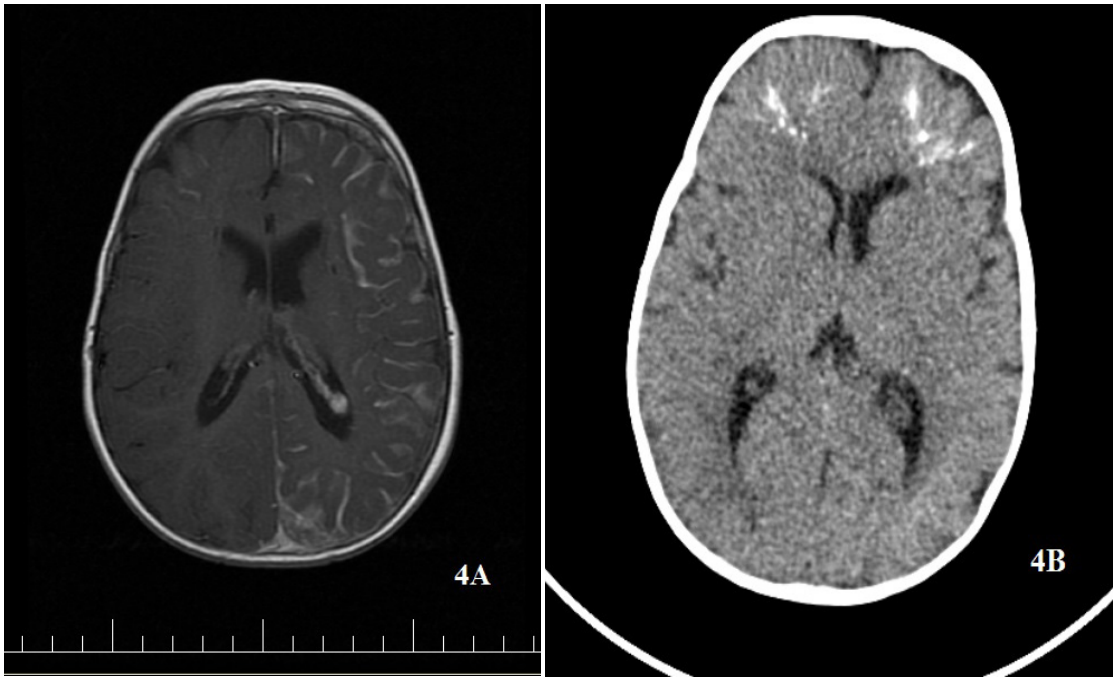

Image 4. Left brain hemisphere with pial angiomatosis in a one-year-old child with infantile seizures.
4.A (axial T1 C + MR) shows serpentine leptomeningeal enhancement of the left hemisphere and engorgement of the choroid plexus.
4.B (axial Brain NECT) showing subcortical WM calcification in bilateral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

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

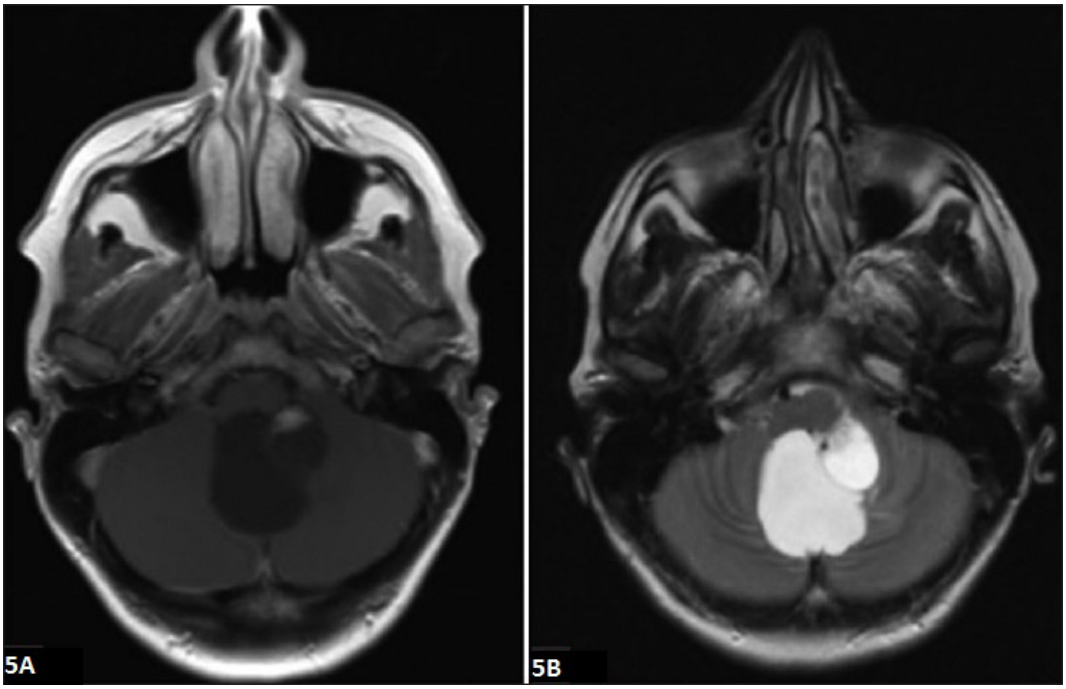

Image 5A. (axial T1 C+) shows hyperintense nodule into a peritumoral cyst in the cerebellum and
5B. (axial T2 C+) shows a strongly enhancing solid tumor nodule in a patient with hemagioblastoma and family history of Von Hippel Lindau disease [23]

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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