We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Chapter 5

Phakomatoses and Their Tumors: Genetics and New Treatment Options

Muhammad Taimur Malik,
Mohammed Faraz Majeed and Scott G. Turner

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/66207

Abstract

In addition to sporadic primary neoplasms of the central nervous system, several genetic syndromes associated with CNS tumors have been identified. Tuberous sclerosis, neurofibromatosis-1 and -2, and von Hippel–Lindau syndrome belong to a collection of disorders called phakomatoses, which include both CNS tumors and cutaneous manifestations. The underlying genetics of these disorders are being elucidated and offer novel therapies for intervention.

Keywords: genetic, phakomatosis, tuberous sclerosis, neurofibromatosis, von Hippel–Lindau

1. Introduction

Phakomatoses are disorders which, in addition to skin manifestations, can lead to the development of tumors within the central and peripheral nervous systems. Due to extensive organ involvement and the complex genetics pathways involved, treatment options are limited. Some of these genetic disorders involve abnormal neural crest migration or terminal differentiation, and tumor suppressor gene dysfunction. These may exhibit autosomal dominant or X-linked recessive inheritance.

Central nervous system manifestations include seizure, stroke, hearing loss secondary to tumor growth, visual loss secondary to optic gliomas, hydrocephalus, and cognitive deficits, while peripheral manifestations include sensory loss or motor weakness from neurofibromas. The cutaneous manifestations of these disorders are usually ectodermal in origin and can and range from small lesions to involvement of entire dermatomes. The common disorders

INTECH
open science | open minds

© 2017 The Author(s). Licensee InTech. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. CC BY

leading to tumor development are tuberous sclerosis, neurofibromatosis-1 and -2, and von Hippel–Lindau syndrome. Ataxia-telangiectasia and Sturge–Weber syndrome are phakomatoses that do not typically lead to tumor development and will not be discussed here.

2. Tuberous sclerosis

2.1. Introduction

Tuberous sclerosis complex (TSC) is a disorder affecting 1:5000–1:10,000 live births [1] characterized by the formation of hamartomas throughout the brain and skin with the formation of renal, pulmonary, and cardiac tumors [2]. It is thought to be caused by mutations in two genes: TSC1on chromosome 9q34 encoding hamartin [3] and TSC2 on chromosome 16p13 encoding tuberin [4]. These mutations result in varying degrees of upregulation of the mTOR pathway. About 10–15% of TSC patients do not have mutations in TSC1 or TSC2, however. While often inherited in an autosomal dominant fashion, two-thirds of patients have de novo mutations [5].

Patients most often present in the first year of life with seizures, typically focal seizures or infantile spasms. The latter are closely associated with cognitive impairments but they typically respond to vigabatrin [6]. A spectrum of cognitive, behavioral, neuropsychiatric, and intellectual disabilities has been described known as TSC-associated neuropsychiatric disorders (TAND), for which there is currently inadequate screening and no approved treatment [7]. Within the brain are found tubers within the cortex and subependymal nodules (SEN) along the walls of the lateral and third ventricles. SEN may transform into subependymal giant cell astrocytomas (SEGA). Retinal astrocytic hamartomas occur in 30–50% of TSC patients and most remain stable over time. They are typically asymptomatic unless they involve the macula or optic nerve [8].

Approximately, 55–80% of patients with TSC have renal involvement including renal cysts, polycystic kidney disease (PKD), and angiomyolipomas (AML) [9]. The Polycystin-1 gene (PKD-1), mutations in which lead to polycystic kidney disease, is downstream of TSC2 and a TSC2/PKD1 contiguous gene syndrome has been described in which deletions affecting both genes lead to TSC with early-onset renal polycystic disease [10]. AML are benign tumors with components of abnormal blood vessels, immature smooth muscle, and mature adipose tissue. They are often multiple, bilateral, and grow mainly during childhood, remaining relatively stable in adulthood [11]. They are associated with an increased risk of micro- and macroaneurysms [12]. Sequelae of the renal manifestations of TSC include an increased risk of hemorrhage from abnormal vasculature, chronic kidney disease, and hypertension.

In TSC, cardiac rhabdomyomas occur, which are more common in neonates and may spontaneously regress throughout childhood. They occur in 20% of adults with TSC. Most are asymptomatic, though arrhythmias including Wolff-Parkinson-White syndrome or outflow obstruction may occur, warranting treatment [13].

Lymphangioleiomyomatosis is an uncommon progressive cystic lung disease affecting 30% of women and a milder form in 10% of men with TSC, associated with mutations in

http://dx.doi.org/10.5772/66207

the TSC2 gene. Abnormal smooth muscle cells proliferate and infiltrate into alveoli, blood vessels, and lymphatics causing obstructive airway disease and blood vessel and lymphatic obstruction leading to dyspnea, pneumothorax, and chylous pleural effusion [14].

The neurocutaneous manifestations of TSC are present in over 90% of patients and include hypomelanotic macules (87–100%), shagreen patches (20–80%), ungual fibromas (17–87%), and angiofibromas (47–90%) [15].

2.2. Diagnosis

The pathogenesis of TSC is thought to be due in part to changes in neural crest function. Neural crest cells arise from embryonic ectoderm and give rise to a number of diverse cell lineages including melanocytes. Cutaneous lesions, particularly hypomelanotic macules and shagreen patches, are due in part to abnormal segmental melanocytic distribution and the characteristic dermal facial angiofibromas are derived from mesencephalic neural crest. Cortical tubers and hamartomas in the periventricular region and are not neural crest derivatives, however [16].

Cortical tubers are developmental in origin and histologically show effacement of the laminar architecture with gliosis, micro-calcifications, large multinucleated cells with glassy, bright eosinophilic cytoplasm, and dysmorphic neurons. These neurons appear "immature" with poorly differentiated cell processes, abundant eosinophilic cytoplasm, and disrupted orientation within the cortical lamina. These structures are believed to be responsible for seizures in TSC patients [17]. Subependymal nodules (SEN) are neoplasms that develop along the walls of the lateral ventricles and can calcify within the first few years of life. These may subsequently develop into subependymal giant cell astrocytoma [18].

SEGA typically develop from SEN in the first two decades of life and present clinically with worsening epilepsy or increased intracranial pressure from obstructive hydrocephalus. These mixed glioneural tumors tend to be well-circumscribed with a variety of tumor cell morphologies including large pleomorphic, multinucleated gemistocytic astrocytes, and small, spindle-shaped astrocytes as well as giant ganglionic pyramidal cells (**Figure 1**). Perivascular pseudorosettes and calcifications are commonly seen. These benign tumors have a low (1–7%) mitotic index and correspond to WHO grade I. Immunohistochemistry demonstrates immunoreactivity for both glial (S-100 and GFAP) and neural (neurofilament, class III β-tubulin, and synaptophysin) markers, again emphasizing the divergent glioneuronal origin of these tumors [19]. Because the ependyma remains intact over SEGA, dissemination of tumor cells into the CSF is rare.

Radiographically, cortical tubers appear as areas of increased cortical and subcortical intensity on T2-weighted magnetic resonance imaging (MRI) and rarely enhance with gadolinium [20]. In contrast, cerebellar tubers are usually wedge-shaped and distort the architecture of the folia. Up to half are calcified and may enhance with gadolinium. They are not epileptogenic and can change in size or enhancement over the first decade of life. Subependymal nodules are T1 hyper-intense and T2 hypo-intense lesions along the lateral ventricles that often enhance with gadolinium and are described as having the appearance of "candle drip-

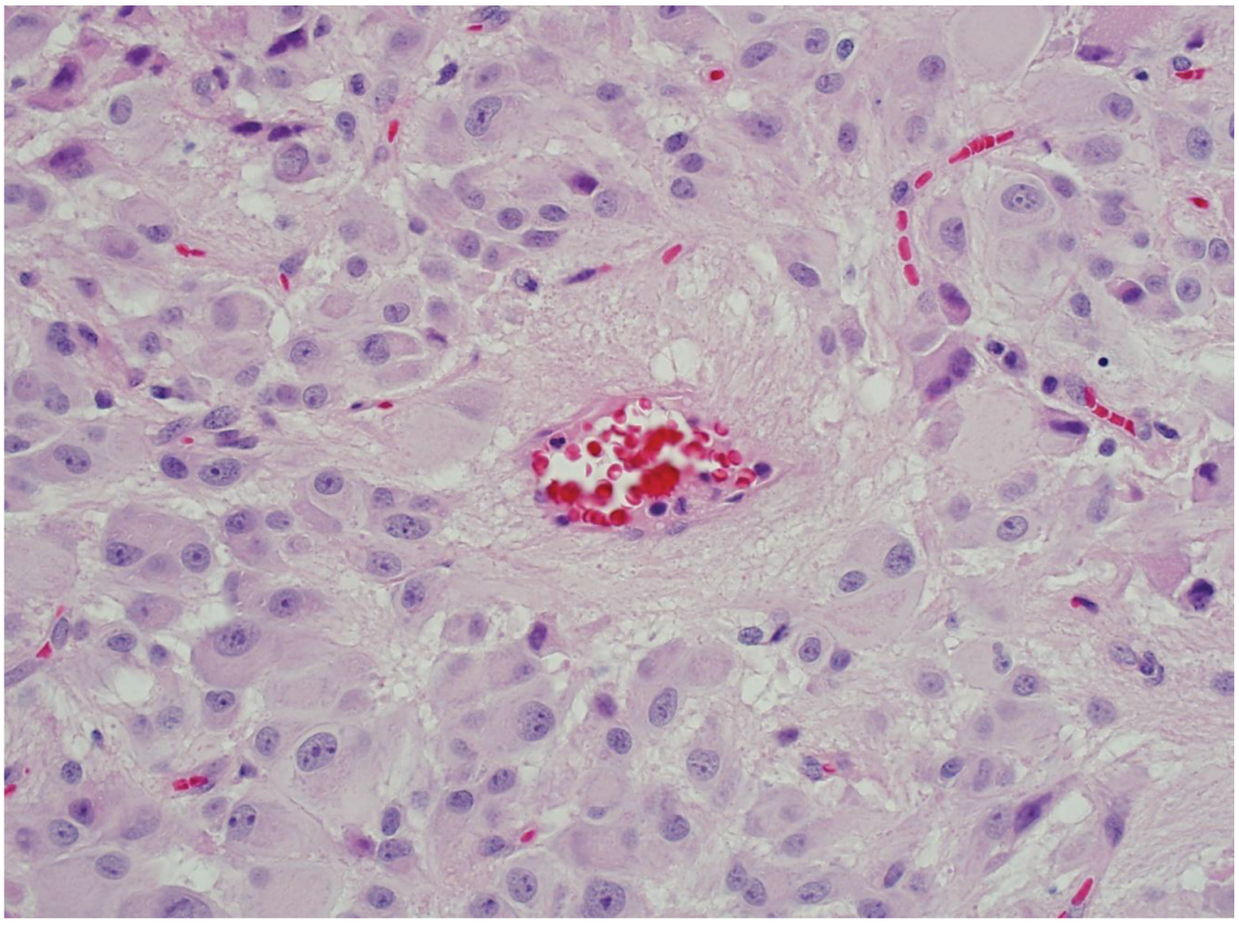


Figure 1. SEGA histology: large cells with abundant cytoplasm and prominent nucleoli, and a perivascular fibrillary area.

pings" [21]. SEGA appear as round to ovoid lesions that are iso- to hypo-intense on T1 MRI and hyper-intense on T2 MRI. They often avidly enhance with gadolinium and calcification and hemorrhage may be seen (**Figure 2**). In addition, radial migration lines may be seen on FLAIR images that represent gliosis resulting from aberrant glial neuronal migration [22].

2.3. Genetics

Mutations in two genes have been identified that lead to TSC. TSC1 on chromosome 9q34 encodes a 130 kDa protein called hamartin and TSC2 on chromosome 16p13 encodes the 200 kDa protein tuberin. TSC2 mutations are more common and are associated with a more severe phenotype [2]. These two proteins form a heterodimeric complex that integrates signals from various pathways involved in regulating cellular responses to environmental stress and energy status (**Figure 3**). TSC2 contains a GTP-activating domain (GAP) that has been shown to activate the small GTPase Rheb [23], which in turn activates mechanistic target of rapamycin complex-1 (mTORC1). mTORC1 is a serine-threonine protein kinase complex whose activation leads to cell growth and differentiation by inhibiting autophagy and promoting protein and lipid synthesis through the phosphatidylinositol 3-kinase-related kinase signaling pathway [24]. TSC1 has no catalytic function and serves to stabilize TSC2 [25].

http://dx.doi.org/10.5772/66207

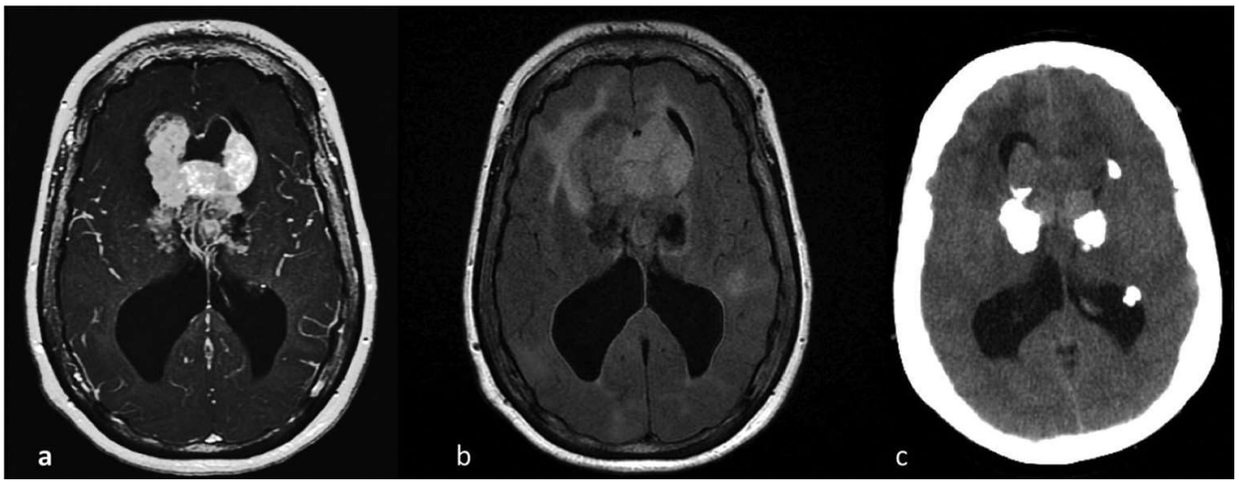


Figure 2. Subependymal Giant Cell Asrocytoma: (a) MRI axial T1 with gadolinium (b) MRI axial T2 FLAIR (c) Head CT showing prominent calcification.

TSC1/2 is regulated by a number of factors. Many growth factors and cytokines act through AKT (protein kinase B), which inhibits TSC1/2 by phosphorylating TSC2 ([26]. Ribosomal S6 kinase (RSK) activates extracellular signal-regulated kinase (ERK), which then phosphorylates and inactivates TSC2. RSK also directly phosphorylates TSC2 [27]. A number of environmental cues lead to TSC1/TSC2 activation. Environmental stress leading to low ATP/AMP ratio leads to activation of AMP-dependent protein kinase (AMPK) that phosphorylates and activates TSC2. Hypoxia induces expression of hypoxia-inducible factor-α (HIF1α) that induces REDD1, which indirectly activates TSC1-TSC2 by removing AKT dependent inhibition [28].

The mTOR1 complex (mTORC1) is a multimeric complex consisting of deptor, PRAS40, raptor, mLST8, mTOR, and TTI1–TEL and effects changes in several important cellular processes [24]. mTORC1 promotes protein synthesis through activation of the translation initiation promoter S6K and through inhibition of the inhibitory mRNA cap binding 4E-BP1. This pathway is thought to play a role in formation of hamartomas. mTORC1 inhibits autophagy through inhibitory phosphorylation of ULK1, preventing formation of the ULK1–ATG13–FIP200 complex required for initiation of autophagy [29]. Increased mTORC1 signaling may cause hypopigmented macules by affecting autophagy during melanogenesis.

Recently, TBC1D7 has been identified as a third subunit in the TSC1/TSC2 complex. This protein does not seem to reflect changes in cellular growth conditions, but loss of TBC1D7 leads to destabilization of TSC1/TSC2 and decreased Rheb-GAP activity [30].

2.4. Treatment

TSC offers a lifetime of treatment challenges for the various manifestations the disease including seizure control, management of cognitive and behavioral effects, and treatment for and monitoring of SEGA. For asymptomatic tumors, surveillance with gadolinium-enhanced MRI every 1–3 year in children and yearly in adults is recommended [31]. Surgery is recommended for symptomatic tumors or asymptomatic tumors in which growth or

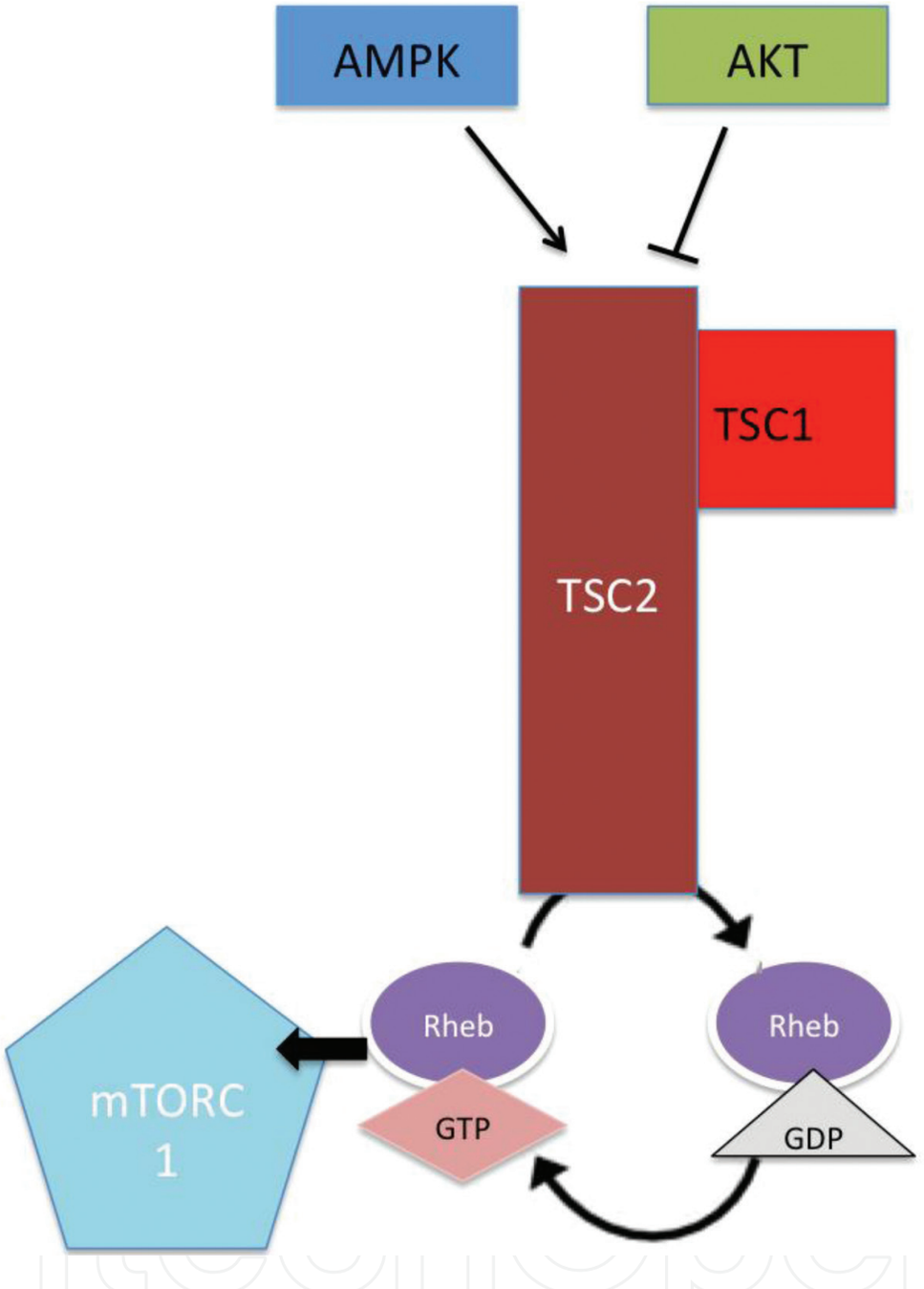


Figure 3. TSC 1 stabilizes TSC2 which is activated by AMPK and inhibited by AKT. The GAP domain of TSC2 inactivates mTORC1 by dephosphorylating GTP associated with Rheb (adapted with permission from Ref. [30]).

increase in ventricle size has occurred. Complete resection is curative, but incomplete resection may lead to tumor regrowth [32, 33], and ventriculoperitoneal shunting is often employed in addition to or in place of tumor resection in order to address the obstructive hydrocephalus resulting from SEGA growth at the foramen of Monro. Though radiation therapy has also been used to treat SEGA, it is not the standard of care and radiation-induced neoplasms have been reported [34].

Because TSC is caused by mutations in tumor suppressor genes leading to upregulation of the mTOR pathway, various mTOR inhibitors have been investigated as possible candi-

dates to treat TSC. Inhibition of mTOR by rapamycin was shown to reduce the size of SEGA [35, 36], renal angiolipomas [37] lymphangioleiomyomatosis [38], and facial angiofibromas [39]. Everolimus [40], a derivative of rapamycin and an inhibitor of mTORC-1, was subsequently chosen as a possible therapy for patients with TSC. In a prospective, open-label Phase 2 study of 28 patients with SEGA, treatment with everolimus for 6 months resulted in reduction in tumor volume and seizure frequency was largely stable to improved [41]. This lead to a larger Phase 3 trial in which 117 adults with SEGA were randomized to receive either everolimus or placebo. Patients in the treatment group were found to have at least a 50% reduction in tumor volume versus the placebo group. Adverse effects were mostly mild and included seizures and stomatitis [35]. Consequently, in 2010, everolimus was FDA-approved for treatment of patients with SEGA that require therapeutic intervention but cannot be curatively resected.

2.5. Future directions

Treatment of TSC involves management of symptomatic SEGA, and recently, everolimus and rapamycin have offered a medical therapy to supplement surgery in treating these slow-growing but clinically important tumors. Currently, these agents are being investigated to manage other manifestations of TSC. Topical rapamycin is being studied to treat facial angiofibromas, and both rapamycin and everolimus are being investigated as treatment for renal angiomyolipoma. As the genetics of TSC are better understood, new molecular targets are likely to be discovered allowing novel pharmacologic agents the ability to improve the quality of life for patients afflicted with TSC.

3. Neurofibromatosis 1

3.1. Introduction

Neurofibromatosis Type 1 (NF1), also known as von Recklinghausen disease, is one of the most common autosomal dominant neurogenic disorders. NF1 affects about 1 in 3000 live births [42] and is sometimes referred as peripheral neurofibromatosis. Although the penetrance is autosomal dominant, there are about 50% sporadic mutations as well. The NF-1 gene is a tumor suppressor gene located on chromosome 17 (17q11.2) [43] and encodes the 250 kDa protein neurofibromas, which is involved in the regulation of the RAS family proto-oncogenes and in the mTOR pathway. The RAS pathway involves a complex downward complex pathway involved in cell differentiation and cell growth through GTP signaling. Mutations in the RAS gene can cause permanent cellular transduction consequently causing increased cellular proliferation causing tumor growth [44].

3.2. Diagnosis

The diagnostic criteria of neurofibromatosis include the presence of two or more of the following:

1. First degree relative with NF1.
2. Axillary of inguinal freckling.
3. Two or more neurofibromas or 1 plexiform neurofibroma.
4. Optic glioma.
5. Osseous lesions.
6. Two or more Lisch nodules.
7. Six or more café au lait spots measuring more than 5 mm in prepubertal individuals or more than 15 mm in postpubertal individuals number [45].

Genetic testing is of diagnostic importance but would not be able to predict the disease severity and outcome. Clinical manifestations of the disease include cutaneous manifestations such as cafe au lait spots, facial, and axillary freckling (Crowe's sign), generalized hyperpigmentation, juvenile xanthogranuloma, Lisch nodules (pigmented hamartomas of the iris), pseudoatrophic macules, and nevus anemicus (a congenital vascular anomaly that presents as a hypopigmented macule or patch). Glomus tumors, benign neoplasms arising from the glomus body of the dermis often occur under the nail or on the fingertips of patients with NF1, as does an increased incidence of melanoma. In addition, NF1 is associated with scoliosis, dysplasia of long bone (sphenoid wing dysplasia), macrocephaly, short stature, learning disabilities, and ADHD. Of course, the hallmark of NF1 is the presence of cutaneous and plexiform neurofibromas, benign (WHO Grade I) nerve sheath tumors arising from nonmyelinating Schwann cells which typically surround small diameter peripheral axons. In contrast, myelinating Schwann cells cover larger diameter peripheral axons and are not tumorigenic. Histologically, neurofibromas consist of elongated wavy cells with small dark oblong nuclei. The tumor is characterized by tortuous proliferation of all components of peripheral nerves including axons, Schwann cells, fibroblasts, and perineural cells. Plexiform neurofibromas are typically larger tumors with more extensive involvement and have the potential to transform into malignant peripheral nerve sheath tumors (MPNST), sarcomas that typically appear in adulthood. About half of MPSNT occur in patients with NF1 [46]. Optic Gliomas are benign tumors of the optic nerve, chiasm, or tract that affect 15–40% of children with NF1 [47]. They typically present with painless vision loss or proptosis and may demonstrate an afferent pupillary defect and optic nerve pallor.

3.3. Genetics

The NF1 gene encodes a large cytosolic protein called neurofibromin and has one of the highest rates of mutations in the human genome. It is about 60 exon and 300 KB of genomic DNA [48]. NF1 is an autosomal dominant disorder, but sporadic mutation occurs in about 50% of patients. The symptoms usually start around age 10 and the penetrance reaches 100% by age 20. NF1 is associated with many other cancers systemically including gliomas, pheochromocytoma, juvenile myelomonocytic leukemia as well as meningioma [49]. NF1 is expressed in neurons, oligodendrocytes, and Schwann cells, and acts as a tumor suppressor by negatively regulating signaling through the Ras pathway by virtue of its GTPase-activating protein (GAP) domain [50]. Over one thousand mutations have been identified in

http://dx.doi.org/10.5772/66207

NF1which lead to upregulation of the Ras signaling pathway leading to cell proliferation, migration, and differentiation.

3.4. Treatment

As per the guidelines from American Academy of Pediatrics children with NF1, routine MRI, EEG, and other imaging of the peripheral nervous system are no longer recommended. Instead they recommend getting routine neurological and ophthalmological examination unless specific other needs arises to image CNS and PNS. With the multitude of symptoms of neurofibromatosis 1, the treatment options available are limited. Surgery may be used to remove painful peripheral neurofibromas but is typically withheld for asymptomatic lesions. Resection is not possible for optic gliomas, though optic sheath fenestration is possible as is debulking of plexiform neurofibromas that involve the orbit.

Although radiation is used to control the local spread of these tumors in the CNS, they are side effects including emergence of other malignancies in the CNS, which limit their use [51]. Neurofibromas are generally considered to be chemoresistant but various chemotherapeutic agents have been investigated to treat MPNST including doxirubicin and ifosfamide but none have shown improvement in recurrence or survival.

3.5. Future directions

Although most of the management of NF1 is symptomatic, clinical trials are being performed to evaluate lovastatin [52] and lamotrigine [53], see whether these agents help with neurocognitive dysfunction. Rapamycin, an MTOR inhibitor, is being investigated as treatment for the plexiform neurofibromas but has not shown an effect on tumor size, though pain is improved with treatment [54, 55].

Imatinib, a tyrosine kinase inhibitor, shows promise in reducing the size of peripheral neurofibromas [56, 57]. Carboplatin and vincristine have also showed promise in treating low-grade gliomas in children with NF1 [58]. Topical vitamin D3 analogues had measurable clinical and histological effects for cutaneous lesions with notable lightening of the lesions and an increase in melanin incontinence.

4. Neurofibromatosis 2

4.1. Introduction

NF2 is also sometimes called central neurofibromatosis due to its predilection towards cranial nerve 8 and meningioma. It accounts for only 5–10% cases of all neurofibromas [59, 60], and there are few if any cutaneous findings. NF2 is an autosomal dominant disorder caused by the mutation in the merlin or schwannomin gene on chromosome 22 (q11–13.1). The precise mechanism as how this tumor suppressor gene manifests the disease is still not clear, but some of the studies have suggested gene activation signaling pathway in glioma tumor suppression [61]. The incidence of this disease is 1:25,000 [62], and it usually presents dur-

ing adolescence with hearing loss and imbalance secondary to vestibular schwannoma. This disease is associated with the development of schwannoma, meningiomas, and other neural tumors. The disease course of the NF2 varies from individuals with mean age of onset of 22 years of age, and mean survival from diagnosis was 15 years and mean age of death at approximately 42 years of age [63]. The most common cause of mortality in NF2 is from rapid tumor growth causing increased intracranial pressure and compression of the brain stem. Morbidity is greatly increased with bilateral deafness and vestibular dysfunction. Usually, the earlier age of onset is associated with rapid growth in the tumor than a later age onset [64].

4.2. Diagnosis

The diagnostic criteria for NF2 (the Manchester criteria) requires one of the following:

1. bilateral Vestibular Schwannoma (VS)
2. one or more 1st degree relative with NF2 + unilateral vestibular schwannoma at <30 years
3. two of the following: multiple meningioma, glioma, schwannoma, juvenile posterior lenticular opacities

NF2 may present clinically with hearing loss or tinnitus or the sequelae of intracranial glioma or meningioma and schwannoma. Ophthalmological manifestations including juvenile posterior subcapsular cataracts, cortical wedge cataracts, retinal hamartomas, and epiretinal membranes. Cutaneous features are similar but less prominent than those in NF1.

Vestibular schwannoma are Grade I tumors, which histologically demonstrate uniformly spindled Schwann cells with Antonin A (cellular fascicular) and Antoni B (myxoid; vacuolated) regions. Nuclear pleomorphism, xanthomatous change, and vascular hyalinization are common, and Rosenthal fibers (bundles of clumped intermediate filament proteins) may be present.

4.3. Genetics

NF2 is an autosomal dominant disorder, although about 50% of the individuals were also found to have spontaneous mutations with no prior family history of NF2. Although the transmission risk is 50% in subsequent generations in parents who have NF2 and is <50% in isolated patients due to mosaics [65]. Tumor linkage analysis genetic testing is a great tool in patients who have sporadic mutation [66].

The NF2 gene product, merlin, is a scaffolding protein linking actin filaments to membrane glycoproteins, and its tumor suppression properties may be due to effects on contact-mediated growth inhibition, though the mechanism is currently poorly understood.

4.4. Treatment

The goal of management of patient with NF2 is to preserve quality of life. Genetic counseling is available to first-degree relatives of affected individuals. Regular MRI screening every 2

http://dx.doi.org/10.5772/66207

years for those high-risk individuals <20-year old and every 3–5 years for those age >20 years should be sufficient. In high-risk patient with positive family history, initial screening can be even started at age 10 years and they are after annual MRI should be sufficient [67]. Regular neurological examination is also of prime importance in these patients. Close surveillance is the key after successful surgery to look for any recurrences.

Surgery for vestibular schwannomas carries the risk of hearing loss [68] and possible injury to the facial nerve [69]. The typical treatment for vestibular schwannoma associated with neurofibromatosis is stereotactic radiosurgery with gamma knife [70]. This type of surgery is associated with better outcome in terms of hearing preservation in about of the patients. This is also associated with reduced recurrence of the tumor in one the study by decreasing the volume of tumor by 33%. [71, 72]. Although a number of complications have also been reported with surgical removal of the VS including air embolism, ICH, Ischemic stroke in the first 3 days of surgery. In one of the study, removal of contralateral VS was associated with increased growth of the other VS after surgery. Due to close proximity of the facial nerve, there are numerous facial nerve complications that can increase the morbidity in surgical patient [73]. Spinal meningiomas and schwannomas if producing neurological complications would need emergent surgery but in asymptomatic patients, they can be closely observed [67].

4.5. Future directions

The vascular endothelial growth factor (VEGF) inhibitors, PTC 299, and bevacizumab [74] have been studied for treatment of vestibular schwannomas in NF2 patients with some improvement in tumor size and hearing function. Lapatinib, which inhibits the tyrosine kinase associated with epidermal growth factor receptor and HER2/neu, has shown promise in adult and pediatric NF2 patients with progressive vestibular schwannomas. Newer gene therapy involving oncolytic recombinant herpes simplex vector has also been shown to reduce volume of the tumor. Curcumin, a HSP 90 inhibitor is also another potential pathway target but still in early part of development [75, 76].

5. Von Hippel–Lindau syndrome

5.1. Introduction

Von Hippel–Lindau (VHL) syndrome is an autosomal dominant disorder characterized by visceral cysts and benign tumors in multiple organ systems that have subsequent potential for malignant change. The disease is named after the German ophthalmologist Eugen von Hippel and the Swedish Pathologist Arvid Lindau. These tumors mainly include hemangioblastomas of CNS and retina (60–65%), renal cysts and carcinomas (40–45%). Tumors that occur less frequently include endolymphatic sac tumor, adrenal pheochromocytoma, epididymal, and broad ligament cystadenomas. A clinical classification system divides individuals who are affected by VHL disease into two groups: Those predominantly without pheochromocytoma

are classified as VHL type 1, and those predominantly with pheochromocytoma classified as VHL type 2. VHL type 2 is further subdivided into type 2A (with renal cancer) and type 2B (without renal cancer). In type 2C, affected patients develop solely pheochromocytoma. The incidence of VHL disease in the United States is approximately 1 case in 36,000 live births. Males and females are affected equally, and it affects people of all ethnic groups. Age at diagnosis varies from infancy to age 60–70 years of age, with an average of 26 years [77].

5.2. Diagnosis

Von Hippel–Lindau (VHL) affects selective organs with the development of hemangioblastomas. This disease should be considered when hemangioblastomas is diagnosed before third decade, spinal cord is involved, and there are multiple other CNS or peripheral lesions. Melon and Rosen established diagnostic criteria for von Hippel–Lindau disease; for diagnosis, a patient must have at least 1 characteristic lesion in the central nervous system, eye, or viscera if there is a family history of an affected first-degree relative, or they must have 2 lesions in the absence of a family history [78]. Diagnosis is established by contrast enhanced MRI of the head and spine which characteristically identifies a solid-enhancing nodule associated with a pseudocyst or syrinx for CNS hemangioblastomas.

Signs and symptoms of hemangioblastomas are determined by tumor site, edema associated with it, cyst formation and spread. Absolute size and the rate of growth does not dictate the symptoms for tumors in all locations and the likely time for symptoms to appear for individual lesions remains unclear because of the saltatory growth pattern exhibited by many tumors [79]. A number of tumor types and organ systems are affected in VHL:

1. CNS hemangioblastomas are the main component of VHL disease that may occur either synchronously or metachronously. Roughly, 80% develop in the brain and 20% in the spinal cord. Growth patterns of these lesions can be saltatory (72%), linear (6%), or exponential (22%). Increased growth of CNS HGB was associated with male sex, younger age group, symptomatic tumors and hemangioblastoma-associated cysts. This indicates the role of biological features related to developmental processes, hormonal factors, other systemic factors, and/or proteasomal processing [79]. Recent studies show that pregnancy has no impact on CNS hemangioblastoma development or progression [80]. Within the brain, the majority are infratentorial, mostly in the cerebellar hemisphere. Supratentorial hemangioblastomas mostly develop in pituitary stalk. Headache, vomiting, and gait disturbances or ataxia is seen with infratentorial tumors; with tumors above the tentorium, symptoms depend on the location of the lesion.

2. Spinal tumors are mostly intradural, involving cervical or thoracic regions most frequently. Most symptom-producing spinal hemangioblastomas are associated with cysts/syringomyelia/syrinx [81]. They usually present with pain; cord compression may lead to sensory and motor loss.

3. Retinal hemangioblastomas, sometimes called retinal angiomas, are histologically identical to CNS hemangioblastomas. They may be the early manifestations of VHL syn-

http://dx.doi.org/10.5772/66207

drome and can occur in childhood with mean age of detection about 25 years. They are mostly located in the temporal periphery of the retina 90% or may develop in the posterior pole (1%) and optic disc (8%) [82]. Retinal hemangioblastomas may be asymptomatic or present with a visual field defect or a loss of visual activity due to retinal detachment, exudation, or hemorrhage. Retinal function tests are helpful in early detection of asymptomatic patients with quiescent retinal angiomas. The number of retinal angiomas does not appear to increase with age; however, there is greater likelihood of vision loss with age.

4. Renal manifestations of VHL include renal cysts or carcinomas. Renal cell carcinoma (RCC) is specifically of the clear cell subtype, which may develop either within a cyst or in the surrounding parenchyma. It occurs in 70% of affected individuals by sixth decade. RCC occurring in VHL is known to have similar growth kinetics as those of sporadic one [83]. A hallmark feature of clear cell renal cell carcinoma is that cells undergo a metabolic shift consistent with the Warburg effect. It is a leading cause of mortality in VHL syndrome, therefore, renal screening is very important [84].

5. Pancreatic cysts: Most pancreatic lesions in VHL are simple cysts that can be numerous in individuals with VHL. They rarely cause endocrine or exocrine insufficiency. Cysts in the head of the pancreas cause biliary obstruction.

6. Neuroendocrine tumors: 5–17% of individuals with VHL develop neuroendocrine tumors of the pancreas. They are not usually hormonally active and are slow growing. Malignant behavior has been observed in tumors >3 cm [85].

7. Pheochromocytoma: These may present with sustained or episodic hypertension or be totally asymptomatic, detected incidentally by an abdominal imaging procedure. Pheochromocytomas are usually located in one or both adrenal glands. They are usually benign, but malignant behavior has been reported.

8. Endolymphatic sac tumors: These are seen in approximately 10–16% of individuals with VHL syndrome, and in some instances, the associated uni- or bilateral hearing loss is the initial feature of the syndrome [86]. The onset of hearing loss is typically sudden; severity varies, but it is often severe to profound [87]. Vertigo or tinnitus is the presenting complaint.

Epididymal and broad ligament cystadenomas: Epididymal or papillary cystadenomas are relatively common in males with VHL syndrome. They rarely cause problems, unless bilateral, in which case they may result in infertility. The equivalent, much less common, lesion in women is a papillary cystadenoma of the broad ligament.

5.3. Genetics

VHL is caused by mutations of the VHL tumor suppressor gene on the short arm of chromosome 3 (3p25–26), and there are over 1500 known mutations to date. The VHL protein regulates the function of hypoxia inducible factor alpha (HIFα) by ubiquitinating it, leading to its degradation

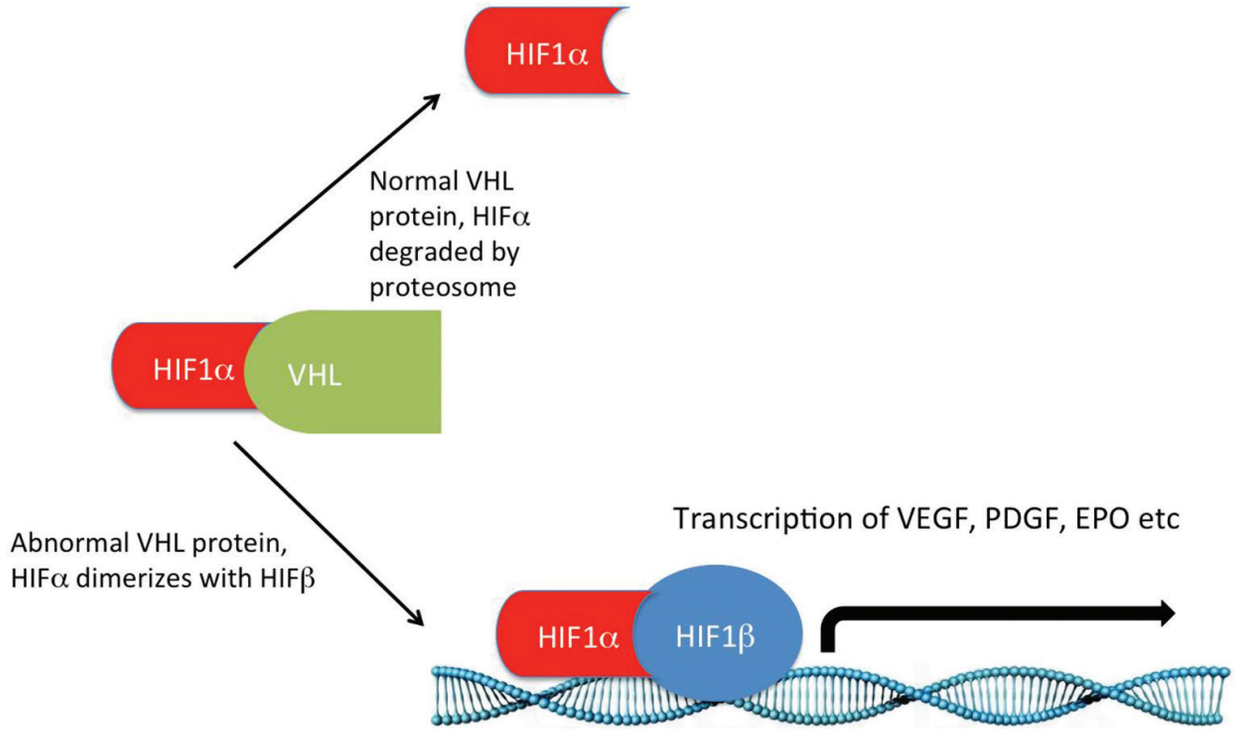


Figure 4. VHL binds to HIFα targeting it for proteosome degradation. With abnormal VHL protein, HIFα dimerizes with HIFβ and activates transcription of a number of genes involved in cell growth and differentiation (adapted with permission from Ref. [99]).

[88]. In VHL, HIFα is not degraded and instead dimerizes with HIFβ to activate the transcription of a number of genes including vascular endothelial growth factor, platelet-derived growth factor B, and erythropoietin [89] leading to multiple tumor types in various organ systems (**Figure 4**).

5.4. Treatment

CNS Hemangioblastomas: Surgery is the treatment of choice. The correct use of microsurgical techniques and thorough understanding of the anatomy yields satisfactory results with minimal morbidity and maximum functional recovery. Outcome depends upon the neurological status before surgery, site, and size of lesion [90]. Favorable results can be achieved by careful dissection of the tumor and preoperative embolization to prevent hemorrhage. The use of intraoperative ICG video angiography in recent years is very helpful for easily locating the minor feeding arteries and maintaining normal perfusion especially in spinal hemangioblastoma surgery [91]. Radiation may be considered if surgery is not suitable. Current medical therapy includes Bevacizumab, Vorinostat, and Dovitinib [92]. Extended periods of follow-up (5 years or more) are necessary to accurately assess the efficacy of nonsurgical therapies, such as chemotherapy and radiation therapy, and tumor stability. Current guidelines recommend that asymptomatic patients who present with a primary spinal cord tumor undergo observation. Symptomatic patients should undergo surgical resection as it promises acceptable rates of neurological improvements

Retinal hemangioblastomas: Most ophthalmologists favor prospective treatment of retinal (but not optic nerve) angiomas to avoid blindness. Laser photocoagulation is the treatment

http://dx.doi.org/10.5772/66207

of choice for retinal capillary hemangiomas in the peripheral areas with a diameter of less than one-fourth of a disc. Cryotherapy is suitable for larger peripheral lesions. Vitrectomies may be useful for cases in which tractional retinal detachment has occurred. Despite being the mainstays of treatment, these procedures have their limitations; therefore, PDT (photodynamic therapy) and intravitreal anti-vascular endothelial growth factor (VEGF) are being considered as treatment options. PDT can be helpful in reducing macular edema associated with RCH (retinal capillary hemangioma); however, it has limitations especially for juxtapapillary tumors [93]. VEGF has been tried recently, but the outcomes are variable [94].

Renal Tumors: Patients with clear cell renal cell carcinoma have limited therapeutic options, as it is unresponsive to chemotherapy and is highly resistant to radiation. Surgery is the best option for renal cell carcinoma. Depending on the size and location of the tumor, nephron-sparing or partial nephrectomy may be possible without compromising survival. Renal transplantation has been successful in individuals in whom bilateral nephrectomy was necessary. Interleukin-2 (IL-2) therapy has proved to be effective in patients with metastatic RCC [95].

Pheochromocytomas: Surgical removal of the tumor has favorable outcome with few recurrences. Partial adrenalectomy is the treatment of choice in children and early screening is recommended [96].

Pancreatic cysts and neuroendocrine tumors: Pancreatic cysts do not require surgical removal; however, tumor needs surgical resection if there is a high risk of metastasis [97].

For VHL associated hemangioblastomas, yearly investigation for craniospinal hemangioblastoma by MRI and yearly screening and follow-up for retinal angiomas is recommended. Annual abdominal ultrasound with triennial CT imaging for abdominal masses is postulated. Annual audiometry is to be performed for possible endolymphatic sac tumor; detailed radiographic imaging of the skull base should be performed upon abnormality in auditory testing. Investigations for cystadenomas of the epididymis and broad ligament only are mandatory on indication. Annual investigation for pheochromocytoma is recommended [98].

5.5. Future directions

Extensive studies, assessing the efficacy of various drugs are in different phases of clinical trials. It includes the role of 17AAG (17-allylamino 17-demethoxygeldanamycin) on RCC and the effects of Sunitinib in VHL patients who are unresponsive to conventional treatment. EYE001 is an experimental drug that seems to have promising results for the treatment of retinal HBG and associated vision loss by decreasing VEGF production.

6. Conclusion

The phakomatoses constitute a complex group of neurocutaneous syndromes with cutaneous, ocular, and neural involvement. Mutations have been identified in a variety of genes affecting multiple aspects of cell cycle regulation including kinase signaling cascades such as

mTOR and Ras as well as transcription factors. Due to the multitude of disease manifestations in multiple organ systems, treatment options are limited. A more complete understanding of the molecular mechanisms underlying these important disorders will lead to the identification of molecular targets for the development of new pharmacologic and biologic therapies.

Author details

Muhammad Taimur Malik, Mohammed Faraz Majeed and Scott G. Turner*

*Address all correspondence to: sgturner@geisinger.edu

Department of Neurology, Geisinger Medical Center, Danville, PA, USA

References

[1] Osborne JP, Fryer A, Webb D. Epidemiology of tuberous sclerosis. Ann N Y Acad Sci. 1991;615:125.

[2] Curatolo P, Bombardieri R, Jozwiak S. Tuberous sclerosis. Lancet. 2008;372(9639):657.

[3] van Slegtenhorst M et al. Identification of the tuberous sclerosis gene TSC1 on chromosome 9q34. Science. 1997;277:805–808.

[4] European Chromosome 16 Tuberous Sclerosis Consortium. Identification and characterization of the tuberous sclerosis gene on chromosome 16. Cell. 1993;75:1305–1315.

[5] Niida Y et al. Survey of somatic mutations in tuberous sclerosis complex (TSC) Hamartomas suggests different genetic mechanisms for pathogenesis of TSC lesions. AJHG. 2001;69(3):493–503.

[6] Curatolo P. Neurological manifestations of tuberous sclerosis complex. Childs Nerv Syst. 1996;12:15–21.

[7] deVries, PJ et al. Tuberous sclerosis associated neuropsychiatric disorders (TAND) and the TAND checklist. Pediatr Neurol. 2015;52:25–35.

[8] Rowley SA, O'Callaghan FJ, and Osborne JP. Ophthalmic manifestations of tuberous sclerosis: a population based study. Br J Ophthalmol. 2001;85:420–423.

[9] Rakowski SK, Winterkorn EB, Paul E, Steele DJ, Halpern EF, Thiele EA. Renal manifestations of tuberous sclerosis complex: inci- dence, prognosis, and predictive factors. Kidney Int. 2006;70:1777–1782.

[10] Martignoni G et al. Renal disease in adults with TSC2/PKD1 contiguous gene syndrome. Am J Surg Pathol. 2002;26(2):198–205.

[11] Pode D, Meretik S, Shapiro A, Caine M. Diagnosis and management of renal angiomyolipoma. Urology. 1995;25:461–467.

[12] Adler J, Greweldinger J, Litzky G. "Macro" aneurysm in renal angiomyolipoma: two cases, with therapeutic embolization in one patient. Urol Radiol. 1984;6:201–203.

[13] Harding CO, Pagon RA. Incidence of tuberous sclerosis in patients with cardiac rhabdomyoma. Am J Med Genet. 1990;37:443–446.

[14] Johnson SR et al. Review panel of the ERS LAM task force. European Respiratory Society guidelines for the diagnosis and management of lymphangioleiomyomatosis. Eur Respir J. 2010;35(1):14–26.

[15] Northrup H and the International Tuberous Sclerosis Complex Consensus Group. Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol. 2013;49:243–254.

[16] Sarnat HB, Flores-Sarnat L. Embryology of the neural crest: its inductive role in the neurocutaneous syndromes. J Child Neurol. 2005;20(8):637–643.

[17] Mühlebner A, van Scheppingen J, Hulshof HM, Scholl T, Iyer AM, Anink JJ, et al. Novel histopathological patterns in cortical tubers of epilepsy surgery patients with tuberous sclerosis complex. PLoS One. 2016;11(6):e0157396. doi:10.1371/journal.pone.0157396

[18] Fukutani Y, Yasuda M, Saitoh C, Kyoya S, Kobayashi K, Miyazu K, Nakamura I. An autopsy case of tuberous sclerosis. Histological and immunohistochemical study. Histol Histopathol. 1992;7(4):709–714.

[19] Buccoliero AM, Franchi A, Castiglione F, Gheri CF, Mussa F, Giordano F, Genitori L, Taddei GL. Subependymal giant cell astrocytoma (SEGA): Is it an astrocytoma? Morphological, immunohistochemical and ultrastructural study. Neuropathology. 2009;29(1):25–30.

[20] Braffman BH, Bilaniuk LT, Naidich TP, et al. MR imaging of tuberous sclerosis: pathogenesis of this phakomatosis, use of gadopentetate dimeglumine, and literature review. Radiology. 1992;183:227–238.

[21] Vézina G. Neuroimaging of phakomatoses: overview and advances. Pediatr Radiol. 2015;45(Suppl 3):S433–S442.

[22] Manoukian SB and Kowal DJ. Comprehensive imaging manifestations of tuberous sclerosis. Am J Roentgenol. 2015;204:933–943.

[23] Inoki K, Li Y, Xu T, and Guan K-L. Rheb GTPase is a direct target of TSC2 GAP activity and regulates mTOR signaling. Genes Dev. 2003;17(15):1829–1834.

[24] Laplante, M and Sabatini DM. mTOR signaling at a glance. Cell Science. 2009;122:3589–3594.

[25] Chong-Kopera H, Inoki K, Li Y, Zhu T, Garcia-Gonzalo FR, Rosa JL, Guan KL. TSC1 stabilizes TSC2 by inhibiting the interaction between TSC2 and the HERC1 ubiquitin ligase. J Biol Chem. 2006;281(13):8313–8316.

[26] Huang J and Manning BD. A complex interplay between Akt, TSC2 and the two mTOR complexes. Biochem Soc Trans. 2009;37(Pt 1):217–222.

[27] Huang J and Manning BD. The TSC1–TSC2 complex: a molecular switchboard controlling cell growth. Biochem J. 2008;412(2):179–190.

[28] Inoki K, Zhu T, Guan KL. TSC2 mediates cellular energy response to control cell growth and survival. Cell. 2003;115(5):577–590.

[29] Jung CH, Ro S-H, Cao J, Otto NM and Kim DH. mTOR regulation of autophagy. FEBS Lett. 2010;584(7):1287–1295.

[30] Dibble CC, Elis W, Menon S, Qin W, Klekota J, Asara JM, Finan PM, Kwiatkowski DJ, Murphy LO, Manning BD. TBC1D7 is a third subunit of the TSC1-TSC2 complex upstream of mTORC1. Mol Cell. 2012;47(4):535–546.

[31] Hyman MH, Whittemore VH. National Institutes of Health consensus conference: tuberous sclerosis complex. Arch Neurol. 2000;57(5):662–665.

[32] Goh S, Butler W, Thiele EA. Subependymal giant cell tumors in tuberous sclerosis complex. Neurology. 2004;63(8):1457–1461.

[33] Cuccia V, Zuccaro G, Sosa F, Monges J, Lubienieky F, Taratuto AL. Subependymal giant cell astrocytoma in children with tuberous sclerosis. Childs Nerv Syst. 2003;19(4):232–243.

[34] Matsumura H, Takimoto H, Shimada N, Hirata M, Ohnishi T, Hayakawa T. Glioblastoma following radiotherapy in a patient with tuberous sclerosis. Neurol Med Chir (Tokyo). 1998;38(5):287–291.

[35] Franz DN, Leonard J, Tudor C, et al. Rapamycin causes regression of astrocy- tomas in tuberous sclerosis complex. Ann Neurol. 2006;59:490–498.

[36] Koenig MK, Butler IJ, Northrup H. Regression of subependymal giant cell astrocytoma with rapamycin in tuberous sclerosis complex. J Child Neurol. 2008;23:1238–1239.

[37] Wienecke R, Fackler I, Linsenmaier U, Mayer K, Licht T, Kretzler M. Antitumoral activity of rapamycin in renal angiomyoli- poma associated with tuberous sclerosis complex. Am J Kidney Dis. 2006;48(3):e27–e29.

[38] Morton JM, McLean C, Booth SS, Snell GI, Whitford HM. Regression of pulmo- nary lymphangioleiomyomatosis (PLAM)- associated retroperitoneal angiomyolipoma post-lung transplantation with rapamycin treatment. J Heart Lung Transplant 2008;27:462–465.

[39] Hofbauer GF et al. The mTOR inhibitor rapamycin significantly improves facial an- giofibroma lesions in a patient with tuberous sclerosis. Br J Dermatol. 2008;159:473–475.

[40] Easton JB, Houghton PJ. mTOR and cancer therapy. Oncogene. 2006;25:6436–6446.

[41] Krueger DA et al. Everolimus for subependymal giant-cell astrocytomas in tuberous sclerosis. N Engl J Med. 2010;363:1801–1811.

[42] Friedman JM. Epidemiology of neurofibromatosis type 1. Am J Med Genet. 1999;89(1):1–6.

[43] Shen MH. Molecular genetics of neurofibromatosis type 1. J Med Genet. 1996;33:2–17.

[44] Johnson MR. Inactivation of NF1 gene in human melanoma and neuroblastoma cell lines without impaired regulation of GTP.Ras. PNAS. 1993;90:5539–5543.

[45] DeBella K, Szudek J. Use of National institutes of Health criteria for diagnosis of neurofibromatosis 1 in children. Pediatrics. 2000;105:608–614.

[46] D'Agostino AN et al. Sarcomas of the peripheral nerves and somatic soft tissues associated with multiple neurofibromatosis (Von Recklinghausen's disease). Cancer. 1963;16:1015–1027.

[47] Listernick R, Charrow J, Greenwald MJ, Esterly NB. Optic gliomas in children with neurofibromatosis type 1. J Pediatr. 1989;5:788–792.

[48] Gutmann DA, Collins FS. Recent progress toward understanding the molecular biology of von Recklinghausen neurofibromatosis. Ann Neurol. 1992;31(5):555–561.

[49] Fahsold R et al. Minor lesion mutational spectrum of the entire NF1 gene does not explain its high mutability but points to a functional domain upstream of the GAP-related domain. Am J Hum Genet. 2000;66(3):790–818.

[50] Corral T, Jiménez M, Hernández-Muñoz I, Pérez de Castro I, Pellicer A.NF1 modulates the effects of Ras oncogenes: evidence of other NF1 function besides its GAP activity. J Cell Physiol. 2003;197(2):214–224.

[51] Packer RJ, Gutmann DH, Rubenstein D, et al. Plexiform neurofibromas in NF1. Neurology. 2002;58(10):1461–1470.

[52] Mainberger F, Jung NH, Zenker M, et al. Lovastatin improves impaired synaptic plasticity and phasic alertness in patients with neurofibromatosis type 1. BMC Neurol. 2013;13:131.

[53] Effect of Lamotrigine on Cognition in NF1 [internet]. 2016. Available from: https://clinicaltrials.gov/ct2/show/NCT02256124 [Accessed: 2016-08-30].

[54] Bhola P, Banerjee S, Mukherjee J, et al. Preclinical in vivo evaluation of rapamycin in human malignant peripheral nerve sheath explant xenograft. Int J Cancer. 2010;126(2):563–571.

[55] Hua C, Zehou O, Ducassou S, Minard-Colin V, Hamel-Teillac D, Wolkenstein P, Valeyrie-Allanore L. Sirolimus improves pain in NF1 patients with severe plexiform neurofibromas. Pediatrics. 2014;133(6):e1792–e1797.

[56] Demestre M, Herzberg J, Holtkamp N, et al. Imatinib mesylate (Glivec) inhibits Schwann cell viability and reduces the size of human plexiform neurofibroma in a xenograft model. J Neurooncol. 2010;98(1):11–19.

[57] Robertson KA, Nalepa G, Yang FC, et al. Imatinib mesylate for plexiform neurofibromas in patients with neurofibromatosis type 1: a phase 2 trial. Lancet Oncol. 2012;13(12):1218–1224.

[58] Packer RJ, Ater J, Allen J, Phillips P, Geyer R, Nicholson HS, Jakacki R, Kurczynski E, Needle M, Finlay J, Reaman G, Boyett JM. Carboplatin and vincristine chemotherapy for children with newly diagnosed progressive low-grade gliomas. J Neurosurg. 1997;86(5):747–754.

[59] Evans DR. Neurofibromatosis type 2 (NF2): A clinical and molecular review. Orphanet J Rare Dis. 2009;4:16.

[60] Viskochil, D. Neurofibromatosis: A Handbook for Patients, Families, and Healthcare Professionals. Am J Hum Genet. 2005. 77: 681.

[61] Yau YK, Murray LB, Houshmandi SS, Xu Y, Gutmann DH, Yu Q. Merlin is a potent inhibitor of glioma growth. Cancer Res. 2008;68(14):5733–5742.

[62] Martuza RL, Ojemann RG. Bilateral acoustic neuromas: clinical aspects, pathogenesis and treatment. Neurosurgery. 1982;10(1):1–12.

[63] Evans DG, Huson SM, Donnai D, et al. A genetic study of type 2 neurofibromatosis. II. Guidelines for genetic counseling. J Med Genet. 1992;29(12):847–852.

[64] Kanter WR, Eldridge R. Maternal effect in central neurofibromatosis. Lancet. 1978;2 (8095):903.

[65] Selvanathan SK, Shenton A, Ferner R, et al. Further genotype-phenotype correlations in neurofibromatosis 2. Clin Genet. 2010;77(2):163–170.

[66] Evans DG, Bourn D, Wallace A, Ramsden RT, Mitchell JD, and Strachan T. Diagnostic issues in a family with late onset type 2 neurofibromatosis. J Med Genet. 1995;32(6):470–474.

[67] Gutmann DH, Aylsworth A, Carey JC, et al. The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2. JAMA. 1997;278(1):51–57.

[68] Temple RH, Axon PR, Ramsden RT, Keles N, Deger K, Yucel E. Auditory rehabilitation in neurofibromatosis type 2: a case for cochlear implantation. Acta Otolaryngol. 2009;129(9):971–975.

[69] Evans DG, Huson SM, Donnai D, et al. A genetic study of type 2 neurofibromatosis in the United Kingdom. I. Prevalence, mutation rate, fitness and confirmation of maternal transmission effect on severity. J Med Genet. 1992;29(12):841–846.

[70] Hasegawa T, Kida Y, Kobayashi T, Yoshimoto M, Mori Y, Yoshida J. Long-term outcomes in patients with vestibular schwannomas treated using gamma knife surgery: 10 year follow up. J Neurosurg. 2005;102(1):10–16.

[71] Phi JH, Kim DG, Chung HT, Lee J, Paek SH, Jung HW. Radiosurgical treatment of vestibular schwannomas in patients with neurofibromatosis type 2: tumor control and hearing preservation. Cancer. 2009;115(2):390–398.

[72] Sharma MS, Singh R, Kale SS, Agrawal D, Sharma BS, Mahapatra AK. Tumor control and hearing preservation after Gamma Knife radiosurgery for vestibular schwannoma in neurofibromatosis type 2. J Neurooncol. 2010;98(2):265–270.

[73] Acoustic Neuroma. NIH Consensus Statement Online. 1991.9(4):1–24.

[74] Wong HK, Lahenranta J, Kamoun WS, et al. Anti-vascular endothelial growth factor therapies as a novel therapeutic approach to treating neurofibromatosis-related tumors. Cancer Res. 2010;70(9):3483–3493.

[75] Angelo LS, Wu JY, Meng F, et al. Combining curcumin (diferuloylmethane) and heat shock protein inhibition for neurofibromatosis 2 treatment: analysis of response and resistance pathways. Mol Cancer Ther. 2011;10(11):2094–2103.

[76] Tanaka K, Eskin A, Chareyre F, et al. Therapeutic potential of HSP90 inhibition for neurofibromatosis type 2. Clin Cancer Res. 2013;19(14):3856–3870.

[77] Kim JJ, Rini BI, Hansel DE. Von Hippel Lindau syndrome. Adv Exp Med Biol. 2010;685:228–249.

[78] Melmon KL., Rosen SW. Lindau's disease: review of the literature and study of a large kindred. Am J Med. 1964;36:595–617.

[79] Lonser RR et al. Prospective natural history study of central nervous system hemangioblastomas in von Hippel-Lindau disease. J Neurosurg. 2014;120(5):1055–1062.

[80] Ye DY et al. Effect of pregnancy on hemangioblastoma development and progression in von Hippel-Lindau disease. J Neurosurg. 2012;117(5):818–824.

[81] Wanebo JE, Lonser RR, Glenn GM, Oldfield EH. The natural history of hemangioblastomas of the central nervous system in patients with von Hippel-Lindau disease. J Neurosurg. 2003;98:82–94.

[82] Maher ER et al. von Hippel-Lindau disease: a clinical and scientific review. Eur J Hum Genet. 2011;19(6):617–623.

[83] Bausch B et al. Renal cancer in von Hippel-Lindau disease and related syndromes. Nat Rev Nephrol. 2013;9(9):529–538.

[84] Asserraji M and El Kharras A. From headache to kidney tumor; an example of von Hippel- Lindau disease. J Renal Inj Prev. 2015;4(3):104–106.

[85] Corcos O, Couvelard A, Giraud S, Vullierme MP, O'Toole D, Rebours V, et al Endocrine pancreatic tumors in von Hippel-Lindau disease: clinical, histological, and genetic features. Pancreas. 2008;37:85–93.

[86] Binderup ML, Bisgaard ML, Harbud V, Møller HU, Gimsing S, Friis-Hansen L, Hansen Tv, Bagi P, Knigge U, Kosteljanetz M, Bøgeskov L, Thomsen C, Gerdes AM, Ousager LB, Sunde L; Danish vHL Coordination Group. Von Hippel-Lindau disease (vHL). National clinical guideline for diagnosis and surveillance in Denmark. 3rd edition. Dan Med J. 2013;60(12):B4763.

[87] Choo D, Shotland L, Mastroianni M, Glenn G, van Waes C, Linehan WM, Oldfield EH. Endolymphatic sac tumors in von Hippel-Lindau disease. J Neurosurg. 2004;100(3):480–487.

[88] Kaelin WG. Von Hippel-Lindau disease. Ann Rev Pathol. 2007;2:145–173.

[89] Bader HL, Hsu T. Systemic VHL gene functions and the VHL disease. FEBS Letters. 2012;586(11):1562–1569.

[90] Joaquim AF et al. Intramedullary hemangioblastomas: surgical results in 16 patients. Neurosurg Focus. 2015;39(2):E18.

[91] Takeshima Y et al. Visualization of vascular structure of spinal hemangioblastoma using intraoperative indocyanine green videoangiography and temporary feeder occlusion. Eur Spine J. 2015;24(Suppl 4):S585–S589.

[92] Kim BY, Jonasch E, and McCutcheon IE. Pazopanib therapy for cerebellar hemangioblastomas in von Hippel-Lindau disease: case report. Target Oncol. 2012;7(2):145–149.

[93] Papastefanou VP et al. Photodynamic therapy for retinal capillary hemangioma. Eye. 2013;27:438–442.

[94] Baba T et al. Subretinal hemorrhage after photodynamic therapy for juxtapapillary retinal capillary hemangioma. Case Rep Ophthalmol. 2011;2(1):134–139.

[95] Coventry BJ and Ashdown ML. The 20th anniversary of interleukin-2 therapy: bimodal role explaining longstanding random induction of complete clinical responses. Cancer Manag Res. 2012;4:215–221.

[96] Aufforth RD et al. Pheochromocytoma Screening Initiation and Frequency in von Hippel-Lindau Syndrome. J Clin Endocrinol Metab. 2015;100(12):4498–4504.

[97] Keutgen XM et al. Evaluation and management of pancreatic lesions in patients with von Hippel-Lindau disease. Nat Rev Clin Oncol. 2016;13:537–549.

[98] Bamps S et al. What the neurosurgeon should know about hemangioblastoma, both sporadic and in Von Hippel-Lindau disease: A literature review. Surg Neurol Int. 2013;4:145.

[99] Pavlovich CP and Schmidt LS. Searching for the hereditary causes of renal-cell carcinoma. Nat Rev. 2004; 4:381–393