Neurocutaneous Syndromes and Associated CNS Tumors

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12.1 Introduction

In the Greek language, *Phakos* means spot, mole, or lentil, and phakomatosis suggests the presence of a congenital lesion or birthmark (Berg 1991). Historically, this term was applied to a group of genetic disorders defined by the involvement of the central nervous system (CNS), skin, and one or more body systems. Over time, this group expanded to include over 40 entities, each with its own specific features (Chalhub 1976). This chapter reviews six of the more common neurocutaneous syndromes and the current designation for these disorders, with a particular emphasis on the CNS tumors occurring in each disease: neurofibromatosis types 1 (NF1) and 2 (NF2), tuberous sclerosis (TS), ataxia telangiectasia (AT), von Hippel–Lindau (VHL), and Sturge–Weber syndrome (SWS). Other comprehensive reviews discuss each entity in detail (Ranger et al. 2014; Lin and Gutmann 2013; Karajannis and Ferner 2015; Rovira et al. 2014; Chaudhary and Al-Baradie 2014; Vortmeyer et al. 2013; Sudarsanam and Ardern-Holmes 2014). More up-to-date information on current molecular genetics is also available through the Online Mendelian Inheritance in Man website (http://www.ncbi.nlm.nih.gov/omim/).

Dysplasia caused by specific genetic alterations within normal ectodermal tissue is thought to give rise to the abnormalities seen in the skin and neural tissues of individuals with neurocutaneous syndromes. The same underlying molecular defects predispose affected individuals to further genetic alterations and increased risk of developing a neoplasm. The molecular mechanisms leading to marked variations in disease phenotype remain incompletely understood, but may depend on specific mutation features in the syndrome genes (Sharif et al. 2011; Upadhyaya et al. 2007) as well as on yet unknown modifier genes and environmental factors (Sabbagh et al. 2009). Clinical characterization of these syndromes has improved, accelerated by advances in imaging techniques such as positron emission tomography (PET) and magnetic resonance imaging (MRI) (Cai et al. 2009; Kalantari and Salamon 2008; van Engelen et al. 2008). Imaging is now essential to identify major and minor criteria used for the diagnosis of neurocutaneous syndromes. In many patients, the neuroradiographic features often precede clinically significant findings or patient symptoms. Advanced imaging techniques are also being incorporated into syndrome-specific response criteria for design of new clinical trials in phakomatoses (Widemann et al. 2013).

Research discoveries revealing the molecular pathogenesis of these disorders have spurred multiple clinical trials of targeted therapies tailored to syndrome-specific aberrant signaling pathways. Clinical success using this strategy has revolutionized the management of vestibular schwannomas in NF2 (bevacizumab) and subependymal giant cell astrocytomas in TS (mTOR inhibitors) (Plotkin and Stemmer-Rachamimov 2009; Franz et al. 2013). Numerous other rationally selected, targeted molecular therapies are being evaluated in clinical trials for tumors occurring in patients with neurocutaneous syndromes.

There are several reasons why oncologists should be familiar with the neurocutaneous syndromes. First, these patients are at increased risk of developing CNS tumors. Second, the natural history of these tumors often differs from sporadically occurring versions of the same tumors (Oh et al. 2011; Listernick et al. 2007; Shamji and Benoit 2007). Finally, the incidence of these inherited syndromes is relatively high. Similar to other genetic syndromes and heritable diseases, great variability exists among patients with phakomatoses due in part to mosaicism, expressivity, and genetic penetrance. Such variability exists among patients afflicted with the same neurocutaneous syndrome, even within a single family and among monozygotic twins (Rieley et al. 2011). Genotype–phenotype correlation studies have given further insight into these diseases but have been disappointing with regard to predicting outcome based on specifically identified mutations (Sabbagh et al. 2013; van Slegtenhorst et al. 1999; Becker-Catania et al. 2000). Further complexity is added by spontaneous mutations that result in neurocutaneous syndromes that lack a family history but incur subsequent risk for patients and their progeny.

12.2 Neurofibromatosis Type 1

12.2.1 Epidemiology

NF1, historically known as von Recklinghausen's disease, is an autosomal dominant disease with an estimated incidence of 1:3000–4000, with equal sex distribution, and no apparent ethnic predisposition (Szudek et al. 2000; Korf 2002). It is one of the most common single-gene disorders, with as many as 50 % of cases arising sporadically due to new mutations. The disorder has a high phenotypic inheritance, and therefore, unaffected parents have a low risk of recurrence. Most cases of NF1 can be detected in infancy based on skin abnormalities, which, although subtle, usually intensify with age, especially after puberty. NF1 exhibits nearly 100 % penetrance by 8 years of age (DeBella et al. 2000).

12.2.2 Genetics and Molecular Biology

The *NF1* gene maps to chromosome 17q11.2 and consists of 57 constitutive exons spread over 350 kb of genomic DNA. More than 200 different mutations have been observed in patients with NF1 (Pros et al. 2008). The *NF1* gene encodes for a 2818 amino acid protein referred to as neurofibromin; is expressed in Schwann cells, oligodendrocytes, and neurons; and acts as a tumor suppressor gene. The protein contains a large amino acid segment exhibiting homology to the functional domain of the p21ras GTPase-activating protein. p21ras GTPase inactivates the oncogene p21ras by stimulating its GTPase activity, thus converting the active form of p21ras into its inactive form. Mutations of neurofibromin leading to low or absent expression allow constitutive activation of p21ras and probably account for the many phenotypic abnormalities seen in NF1, including benign and malignant neoplasms. Germline mutation in the *NF1* gene constitutes the first hit in the 2-hit cancer theory. Malignant transformation occurs with additional genetic changes such as mutations in *TP53* or loss of *CDKN2A* or *PTEN* (reviewed in Laycock-van Spyk et al. 2011). Inactivation of neurofibromin has also been shown to alter cellular cAMP levels in neurons via ras-dependent signaling through PKCζ (Anastasaki and Gutmann 2014). It has been suggested that such molecular signaling abnormalities may also underlie the learning disabilities well-described in approximately half of all patients with NF1 (Diggs-Andrews and Gutmann 2013; Szudek et al. 2000).

12.2.3 Diagnostic Criteria and Clinical Features

The clinical features of NF1 are divided into major and minor subgroups (Table 12.1). The most recognizable clinical feature of NF1 is the café au lait spot, a smooth, nonraised, brown discoloration of the skin, which appears before adulthood in 95 % of patients with NF1. Dermal neurofibromas, which arise from Schwann cells, occur in >99 % of patients. These tumors appear during adolescence and increase in number and size with age. Other manifestations seen in patients with NF1 include axillary freckling, Lisch nodules (pigmented hamartomas of the iris), optic gliomas, and bone dysplasias (Szudek et al. 2000; Korf 2002). Other associated symptoms include

Table 12.1 Major and minor features of NF1

Major features	Minor features
Café au lait spots and skin freckling	Macrocephaly
Peripheral neurofibromas	Short stature as growth hormone deficiency found in NF1 patients that do not even have hypothalamic lesions
Lisch nodules (iris hamartomas)	Hypsarrhythmia
Plexiform neurofibromas	Intellectual difficulties (e.g., learning difficulties)
CNS tumors (optic gliomas, spinal neurofibromas)	Epilepsy
Distinctive osseous lesions (ribbon ribs, sphenoid wing dysplasia, pseudarthroses, or thinning of long bone cortex)	Hypertension – may be due to aortic coarctation, renal artery stenosis, or pheochromocytoma

NIH Consensus Development Conference, Neurofibromatosis: Conference Statement, 1988

macrocephaly, vascular changes, short stature, scoliosis, and learning disabilities. As outlined in an earlier NIH meeting (NIH Consensus Development Conference, Neurofibromatosis: Conference Statement 1988), the diagnosis of NF1 is made if a patient has met two or more of the following criteria:

1. Six or more café au lait spots (greatest diameter >5 mm if prepubertal, >15 mm if postpubertal)
2. Two or more neurofibromas of any type or one or more plexiform neurofibromas
3. Freckling in the axilla or inguinal regions (Crowe's sign)
4. Two or more Lisch nodules (iris hamartomas)
5. An optic pathway tumor
6. A distinctive osseous lesion such as sphenoid wing dysplasia or thinning of the cortex of the long bones with or without pseudarthroses
7. First-degree relative (parent, sibling, or offspring) with NF1 by the aforementioned criteria

There is an increased incidence of specific CNS neoplasms in patients with NF1 (Korf 2000; Rosser and Packer 2002). The most common NF1-associated tumors are optic gliomas, especially chiasmatic gliomas, the majority of which are diagnosed in childhood (Turgut et al. 1991; Balestri et al. 1993). Studies suggest that up to 30 % of patients with optic pathway glioma have stigmata of NF1 (Dutton 1994) and 5–25 % of patients with NF1 have signs of optic pathway glioma (Listernick et al. 2007), suggesting that many NF1 patients are asymptomatic and, therefore, might never be diagnosed. If symptomatic, these tumors may present with decreased visual acuity, visual field defects, proptosis, and precocious puberty due to hypothalamic compression. To date, there is no consensus regarding the frequency of follow-up MRIs required, and it can vary from every 3 to 24 months (Listernick et al. 2007). Some studies argue that assessing the visual system is sufficient to follow these patients and that MRI studies are not indicated in patients with no clinical signs of disease progression (Listernick and Charrow 2004; Listernick et al. 2007).

In addition to optic gliomas, NF1 is associated with an increased incidence of parenchymal gliomas, particularly in the brainstem, cerebellar peduncles, globus pallidus, and midbrain. The biologic behavior of brainstem gliomas in patients with NF1 differs significantly from that of lesions with similar appearance in patients without NF1 (Pollack et al. 1996; Listernick et al. 1999). In general, patients with NF1 and brainstem gliomas have better outcomes than nonaffected children (Sevick et al. 1992; Listernick et al. 1994). A recent study identified 23 patients out of 125 with NF1 (18.4 %) who presented with brainstem mass lesions. Reported outcome was favorable; 17/23 untreated and 6/23 treated patients were alive with stable or decreased disease burden on MRI at median follow-up of 67 and 102 months, respectively. Only one previously untreated patient experienced disease progression (Ullrich et al. 2007). Brainstem tumors should not be confused with nonspecific white matter changes, which are frequently found on MRI in patients with NF1 and are of unknown clinical significance (Sevick et al. 1992; van Engelen et al. 2008). These unidentified bright objects are normally not associated with mass effect, edema, or contrast enhancement and tend to decrease in size over time. Besides astrocytomas, CNS neoplasms that occur at higher rates in NF1 patients are ependymomas, meningiomas, and medulloblastomas.

NF1 patients develop not only CNS lesions but also peripheral nervous system tumors. Neurofibromas and schwannomas arise most commonly from major peripheral nerves particularly radial and ulnar nerves. The incidence of symptomatic neurofibromas in NF1 patients is 4 %, and the incidence of asymptomatic but radiographically evident tumors is >25 %. Malignant transformation leads to malignant peripheral nerve sheath tumors. These tumors occur in less than 5 % of children with NF1, but are the leading cause of mortality in adults with NF1 (Rasmussen et al. 2001). Malignant peripheral nerve sheath tumors (MPNST) are chemoresistant sarcomas associated with poor 5-year survival rates despite aggressive therapy. The impact of NF1 diagnosis on the prognosis of

MPNST is controversial (LaFemina et al. 2013; Kolberg et al. 2013; Porter et al. 2009). The clinical signs associated with malignant transformation are rapid growth and/or pain. FDG-PET is increasingly relied upon to identify lesions suspicious for malignant transformation (Benz et al. 2010; Tsai et al. 2012). Surgical resection remains the mainstay of therapy. The other indication for surgical resection is a large tumor that creates a cosmetic problem. Patients with NF1 are also at risk for non-CNS tumors, including Wilm's tumor, rhabdomyosarcoma, leukemia, melanoma, medullary thyroid carcinoma, and pheochromocytoma.

12.2.4 Natural History and Prognosis

NF1 is a progressive disease that can affect almost any organ (Rasmussen et al. 2001; Korf 2002), and overall survival is less than that of the general population (Sorensen et al. 1986; Evans et al. 2011; Duong et al. 2011); however, outcomes remain highly variable even within individual families. The causes of death in NF1 patients include malignant peripheral nerve sheath tumors, CNS tumors, and systemic conditions such as hypertension due to the associated vasculopathies leading to renal artery stenosis. Patients with NF1 are 34 times more likely to have malignant connective tissue or soft tissue neoplasms than non-NF1 individuals (Rasmussen et al. 2001). In population-based cohorts that include children with NF1, a ~4000–8000-fold increased risk of death from MPNST is seen when compared to the non-NF1 population (Evans et al. 2011).

12.2.5 Laboratory Studies

A wide variety of mutations in the NF1 gene have been identified. Current molecular technology is able to identify NF1 mutations in greater than 95 % of cases (Messiaen et al. 2000). Next-generation sequencing has been successfully deployed in the molecular diagnosis of NF1 patients and may facilitate genotyping NF1 mosaic patients as well as identification of second-hit mutations in NF1-associated tumor specimens (Pasmant et al. 2015). However, to date, the majority of cases are identified on a clinical basis, and therefore genetic testing should be reserved for when there is uncertainty in the clinical diagnosis. Prenatal diagnosis is also available for couples with a positive family history of NF1.

12.2.6 Imaging Studies

With MR brain imaging, optic nerve gliomas are easily visible with enlargement of the optic nerve(s), chiasm, and/or optic tract (Fig. 12.1). Asymptomatic optic gliomas are present in up to 20 % of NF1 patients. The extent of involvement is often underestimated with T1-weighted images, while T2-weighted images provide better representation of the involved areas. Contrast enhancement can occur and may be heterogeneous or homogeneous. Brainstem gliomas are relatively common (Aoki et al. 1989; Balestri et al. 1993; Mukonoweshuro et al. 1999; Kornreich et al. 2001; Fischbein et al. 2000). Parenchymal tumors (usually astrocytomas) have a predilection for the thalami and basal ganglia and appear as T2 prolonging mass lesions with variable post-gadolinium enhancement.

Nonenhancing foci of T2 prolongation within deep gray nuclei and the white matter have a poorly understood underlying etiology (Billiet et al. 2014) and can be difficult to distinguish from suspected low-grade brainstem gliomas on MR imaging in the setting of NF1 (Hervey-Jumper et al. 2013). Their natural history is reflective of an indolent process with reports of spontaneous regression. These are most common in the globus pallidus, followed by the cerebellum and brainstem, internal capsules, centrum semiovale, and corpus callosum and occur in up to 60 % of NF1 patients (Fig. 12.2). The T2-weighted signal characteristics are variable.

MRI remains a mainstay modality for detection and surveillance of peripheral neurofibromas in NF1 patients. Recent reports suggest a promising role of whole-body MRI for rapid, comprehensive, and quantitative assessment of

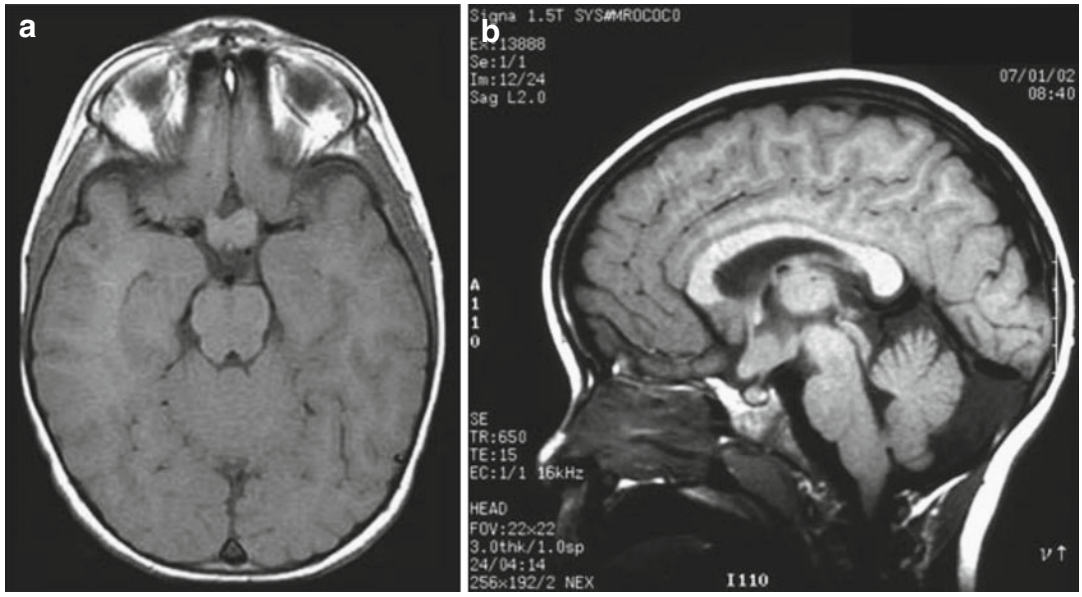

Fig. 12.1 Optic pathway gliomas associated with NF1. (**a**) The T1-weighted axial images show asymmetry of the optic chiasm with the left optic nerve being larger than the right. The mass did not enhance following gadolinium administration. (**b**) A sagittal T1-weighted image shows the thickened chiasm directly above the pituitary gland

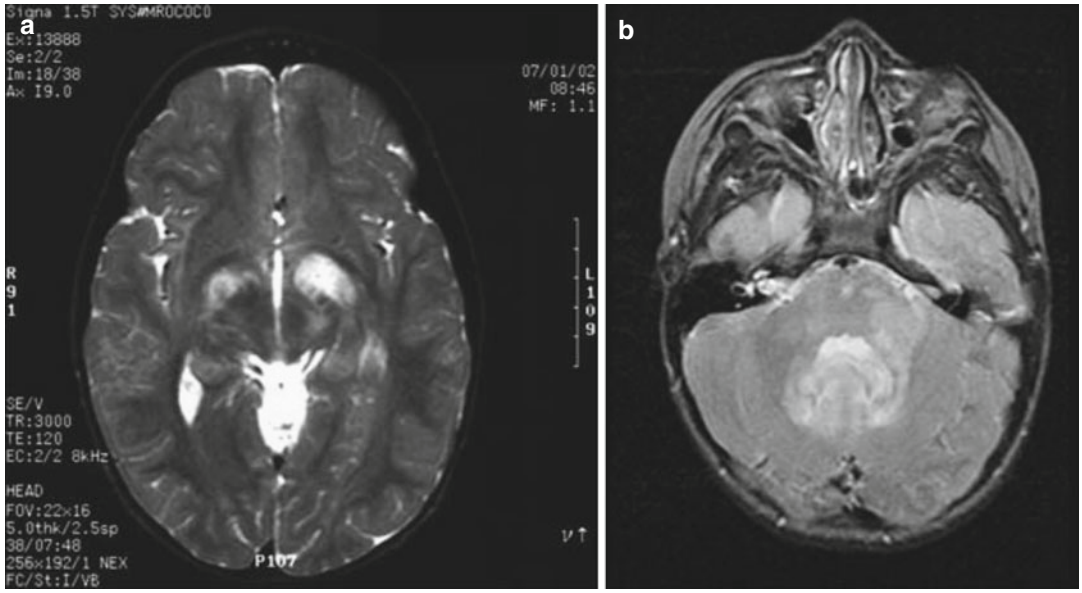

Fig. 12.2 White matter lesions associated with NF1. These lesions are best seen on T2-weighted images. (**a**) In this axial image, there are bilateral lesions (larger on the patient's left side) within the basal ganglia that do not produce much mass effect. These lesions do not enhance following gadolinium administration. (**b**) Similar lesions may be seen in the posterior fossa. Here, the area of T2 prolongation extends from the cerebellar peduncle toward the pons

neurofibroma tumor burden (Plotkin et al. 2012). FDG-PET imaging has shown promise in differentiating MPNST from non-degenerated neurofibromas in the setting of NF1 (Benz et al. 2010; Tsai et al. 2012).

12.2.7 Treatment

Patients with NF1 should have a thorough annual physical examination including visual field testing. Although the value of screening imaging studies is not proven, most patients at some point undergo a screening MRI of the brain and spine. Even if a mass is identified, treatment focuses on symptomatic lesions (Turgut et al. 1991; Pollack et al. 1996). Most optic pathway gliomas associated with NF1 are asymptomatic, and some have been noted to regress spontaneously (Parsa et al. 2001). Pathologically, these tumors are mainly pilocytic astrocytomas, classified as WHO grade I, with more indolent clinical courses than in non-NF1 patients. The role of surgery in patients with optic pathway gliomas remains controversial. Consensus for surgical intervention exists for single-nerve lesions, which cause disfiguring symptoms for patients. Surgery might also be beneficial if there are signs of increased intracranial pressure, mass effect, or hydrocephalus (Medlock et al. 1997; Astrup 2003). Rapidly growing tumors, more frequently located in the hypothalamus and chiasm, benefit from early surgical resection to preserve vision and reduce mass effect (Listernick et al. 2007).

Radiation therapy is discouraged in patients with NF1, mainly due to the development of neurovascular, endocrine and neuropsychological side effects as well as the high risk of developing secondary malignancies (Madden et al. 2014; Grill et al. 1999; Sharif et al. 2006). In a prospective trial of conformal radiation therapy for pediatric low-grade glioma that included 13 patients with NF1, the presence of NF1 was associated with lower baseline intellectual function as compared to non-NF1 patients and with a greater decline in behavioral assessment scores following radiation treatment (Merchant et al. 2009). With respect to secondary malignancy risk, one study showed that three out of five patients with NF1 and optic pathway glioma, who were treated with radiation therapy for disease progression, developed a secondary CNS tumor, whereas none of the patients with sporadic tumors developed a secondary tumor (Singhal et al. 2002). Similarly, in another study of neurofibromatosis patients treated with radiotherapy, local control was achieved with irradiation in three of five low-grade glioma patients, while two patients progressed to high-grade glioma in the radiation field (Wentworth et al. 2009). By contrast, a prospective study of radiation or chemotherapy for progressive pediatric low-grade glioma reported no untoward radiation-associated acute or late effects in ten NF1 patients who had received radiation therapy with a median follow-up of 5.2 years for this subgroup. Only three of these patients demonstrated post-radiation tumor progression (Hernaiz Driever and von Hornstein 2010).

Slow enlargement of optic pathway gliomas clearly demonstrated on serial imaging studies and accompanied by symptoms can be managed by systemic chemotherapy. A recent expert consensus statement recommends nonsurgical treatment of hypothalamic–chiasmatic low-grade gliomas if visual function is threatened or if symptomatic progression is documented. Surgical intervention was not recommended as frontline therapy in the majority of cases (Walker et al. 2013). A retrospective multicenter study of visual outcomes after chemotherapy in 115 patients with NF1-associated optic pathway glioma revealed improved and stable visual acuity after chemotherapy in 32 % and 40 % of patients, respectively (Fisher et al. 2012). A large phase II study found that 22 NF1 patients with low-grade gliomas who were treated with chemotherapy had better overall survival than non-NF1 patients (Gururangan et al. 2002). Patients were treated if they met one or more of the following criteria: (a) >25 % increase in the size of the tumor (Fig. 12.3a, b), (b) papilledema, (c) loss of vision, (d) increase in proptosis, or (e) increase in the diameter of the optic nerve >2 mm. An increased response rate following chemotherapy in NF1-associated pediatric low-grade gliomas as

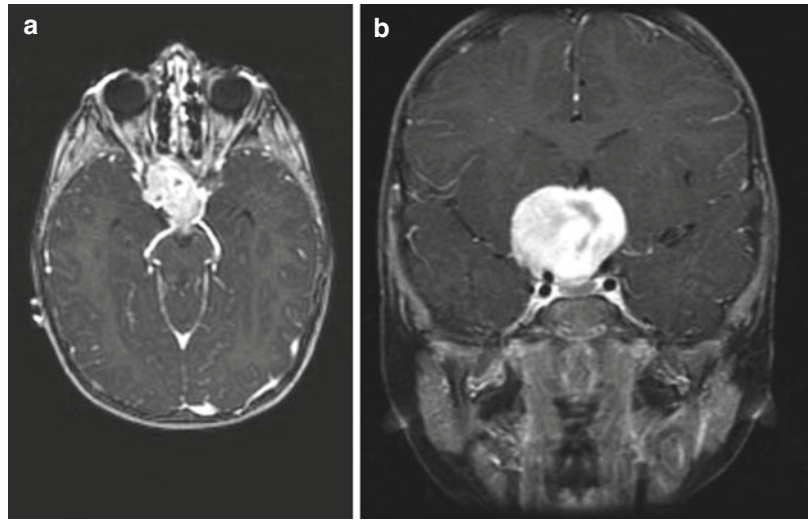

Fig. 12.3 Large optic pathway glioma in a patient with NF1. This 3-year-old-girl presented with visual loss and was noted to have an extremely large optic glioma as seen on axial (**a**) and coronal (**b**) T1-weighted images following contrast administration. The optic chiasm and nerves cannot be differentiated from the tumor. Because of the degree of visual loss, the patient underwent biopsy to confirm the diagnosis and then was started on chemotherapy

compared to sporadic pediatric low-grade gliomas was also observed in the long-term follow-up results of the large HIT-LGG-1996 protocol in Europe (Gnekow et al. 2012) and in preliminary results of the COG protocol A9952 (Kalamarides et al. 2012). It is yet unclear, however, whether the overall favorable prognosis of these lesions in the setting of NF1 is attributable predominantly to increased chemosensitivity versus an intrinsically indolent natural history.

Usually, protocols tailored for low-grade astrocytic tumors are used (see Chap. 1). There have been early reports of promising activity of bevacizumab associated with long-term survival in NF1-associated high-grade glioma (Theeler et al. 2014). Surgery is often required for plexiform neurofibromas that have become disfiguring or painful, and multiple targeted biologic-based approaches have been investigated in recent early phase trials. Unfortunately, many rationally selected agents failed translation from animal models to phase I and phase II trials in the setting of NF1 (Agarwal et al. 2014). However, there have been preliminary signs of promise in phase II trials of the farnesyltransferase inhibitor tipifarnib (Widemann et al. 2014a) and the c-Kit inhibitor imatinib (Robertson et al. 2012) in the treatment of NF1-associated neurofibromas. Encouraging preliminary results have also been seen in a trial of the MEK inhibitor selumetinib in NF1-associated inoperable plexiform neurofibromas (Widemann et al. 2014b). See http://www.ctf.org for ongoing NF1 patient trials.

12.3 Neurofibromatosis Type 2

12.3.1 Epidemiology

NF2 is inherited in an autosomal dominant manner with an incidence of 1:37,000 and has no gender predilection (Mautner et al. 1993; Parry et al. 1994). Generally NF2 patients become symptomatic at puberty or thereafter, but age of onset is highly variable. The mean age of onset of symptoms is approximately 17 years, usually with tinnitus and/or acute hearing loss due to vestibular tumors.

12.3.2 Molecular Biology and Cytogenetics

The *NF2* gene is located on chromosome 22q12, and the protein consists of 595 amino acids. It was identified in 1993 in two different laboratories and named *merlin* and *schwannomin* (Rouleau et al. 1993; Bianchi et al. 1994). The name merlin refers to a high degree of homology with a family of F-actin-binding proteins including *m*oesin, *e*zrin, and *r*adixin (De Vitis et al. 1996a, b).

Merlin localizes at the cell membrane and acts as a membrane-cytoskeletal linker. It can revert Ras-induced malignant phenotypes, indicating that the *NF2* gene product has a tumor suppressor activity. More recently, merlin has been shown to control a broad cellular proliferation signaling program through inhibition of the $CRL4^{DCAF1}$ E3 ubiquitin ligase and modulation of the Hippo signaling pathway by a variety of mechanisms (Cooper and Giancotti 2014; Karajannis and Ferner 2015). Multiple canonical downstream growth signaling pathways including Rac-PAK, PI3K-Akt, FAK-Src, and EGFR-Ras-Erk appear to be negatively regulated by active merlin. Mechanistic links between these canonical pathways and upstream events in the setting of merlin inactivation remain to be fully elucidated.

Despite considerable efforts, it also remains unclear if any of the known merlin-regulated signaling pathways are keys to the development of NF2-associated tumors (Scoles 2008). Mutations leading to the loss of merlin expression are the most common gene defect in meningiomas. A total of 50–60 % of all spontaneous meningiomas and NF2-associated meningiomas have mutations in the *NF2* gene. Schwannomas are caused by loss of merlin expression, whereas only 29–38 % of ependymomas show alteration in merlin expression (Lamszus et al. 2001; Rajaram et al. 2005). Mutations of the *NF2* gene occur not only in neoplasms associated with NF2 but also in 30 % of melanomas and 41 % of mesotheliomas (De Vitis et al. 1996a, b). It remains unclear why *NF2* mutations predispose to the formation of bilateral vestibular schwannomas.

Recently, a third disorder within neurofibromatosis was distinguished as schwannomatosis. This disorder is characterized by the presence of schwannomas of cranial nerves other than the vestibular nerve. This disorder has been associated with two genes on chromosome 22 near the *NF2* locus, *SMARCB1*, and *LZTR1* (Paganini et al. 2015).

12.3.3 Diagnostic Criteria and Clinical Features

Clinical criteria are used to diagnose NF2 (Table 12.2). Bilateral vestibular schwannomas, which are characteristic lesions in patients with NF2, usually present with tinnitus and/or hearing loss (Uppal and Coatesworth 2003). These tumors are found in 96 % of NF2 patients: bilateral in 90 %, and unilateral in 6 %. Vestibular schwannomas were formerly called acoustic neuromas, an inaccurate term because they arise from Schwann cells and typically involve the vestibular rather than the acoustic (cochlear) branch of the eighth cranial nerve. NF2 patients exhibit an overall predilection for tumors of the meninges and Schwann cells and may also present with facial nerve, trigeminal nerve, and multiple spinal nerve schwannomas, as well as meningiomas and retinal hamartomas. Symptoms at time of presentation include hearing loss, tinnitus, and disequilibrium from vestibular schwannomas. NF2 patients under 10 years of age present most commonly with visual deficits or rapidly growing skin tumors.

Table 12.2 NF2 diagnostic criteria

Primary criteria	Additional criteria
Bilateral eighth cranial nerve masses (vestibular schwannomas) seen with imaging techniques	Unilateral vestibular schwannoma *and* any two of glioma, meningioma, neurofibroma, schwannoma, or posterior subcapsular lenticular opacities
Family history of NF2 *and* unilateral vestibular schwannoma *or* any two of glioma, neurofibroma, meningioma, schwannoma, or posterior subcapsular lenticular opacities	Multiple (2 or more) meningiomas *and* unilateral vestibular schwannoma *or* any two of the following schwannoma, glioma, neurofibroma, or cataract

Modified NIH Consensus Criteria, Evans et al. (2005)

NF2 patients develop other central neurofibromas including paraspinal tumors that may compress the spinal cord and present with myelopathy. These lesions are surprisingly common (67–90 %) in patients with NF2 and are a source of major morbidity and mortality (Mautner et al. 1995; Dow et al. 2005). Additional lesions associated with NF2 include posterior subcapsular cataracts (63 %), retinal hamartomas, optic nerve sheath meningiomas, meningiomas, ependymomas (usually spinal cord), gliomas, and trigeminal schwannomas (Mautner et al. 1996).

12.3.4 Natural History and Prognosis

The mean age of onset of symptoms is 17 years, while the mean age of NF2 diagnosis is 22 years. Relentless progression of vestibular schwannomas and other tumors may lead to loss of vision, paresis, and eventual death from brainstem compression (Parry et al. 1994). Overall, NF2 patients have been demonstrated to have a decreased life expectancy as compared to the general population (Wilding et al. 2012). However, the prognosis for NF2 patients is variable, as a spectrum of phenotypes exists. The type of mutation in the *NF2* gene influences the disease severity. Constitutional nonsense and frameshift mutations that cause protein truncation confer a poorer phenotype (Baser et al. 2004; Selvanathan et al. 2010). Early detection offers distinct advantages to the patients as hearing preservation remains a challenge. The diagnosis of NF2 increases the likelihood of developing CNS tumors (schwannomas, meningiomas, gliomas, and neuromas) that may involve the brain, cranial nerves, or spinal cord.

12.3.5 Laboratory Studies

Laboratory diagnosis relies on the presence of DNA mutation in the *NF2* gene and requires linkage studies from DNA derived from at least two affected family members.

12.3.6 Imaging Studies

Schwannomas on CT head scanning are round or ovoid extra-axial masses. They are iso- to mildly hypodense on noncontrast CT scan, unless cystic or hemorrhagic. Meningiomas are dural-based, extra-axial masses, often with an associated dural tail. They are typically isodense to brain on nonenhanced CT scan (Aoki et al. 1989; Mautner et al. 1996; Fischbein et al. 2000).

On MR imaging, schwannomas are iso- to mildly hypointense compared to brain parenchyma on T1-weighted images. They are iso- to hyperintense to brain parenchyma on T2-weighted images. Intense homogeneous enhancement after contrast administration is typically seen (Fig. 12.4a), although areas of cystic change or hemorrhage may lead to heterogeneous enhancement. Large lesions may cause brainstem compression and/or hydrocephalus. The multilobulated-appearing vestibular schwannomas often seen in NF2 have recently been shown to consist of mixed cell populations bearing a variety of somatic NF2 mutations, suggestive of a collision between several distinct tumor clones, which

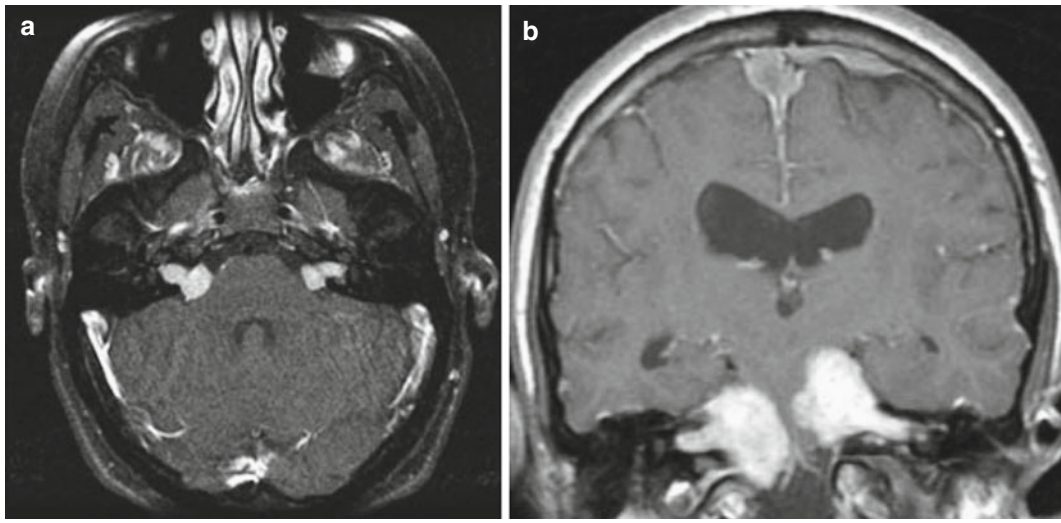

Fig. 12.4 NF2 tumors. (**a**) Typical appearance of bilateral vestibular schwannomas in a teenage girl. On this fat-suppressed T-weighted axial image, the tumors are clearly seen arising from the internal acoustic meatuses on either side. (**b**) This patient has much larger bilateral schwannomas although convexity and falcine meningiomas are also visualized

may account for their relative resistance to treatment (Dewan et al. 2015).

Similar to schwannomas, meningiomas are isointense to gray matter on T1- and T2-weighted images. They usually enhance intensely and homogeneously following gadolinium administration, and calcifications are common (Fig. 12.4b) (Mautner et al. 1996; Fischbein et al. 2000).

12.3.7 Treatment

The best approach to the management of schwannomas remains controversial, although expert consensus recommendations have been published (Blakeley et al. 2011). Hearing loss in the setting of vestibular schwannomas generally progresses slowly, and if the lesions are small and asymptomatic, patients can be followed by serial imaging studies. A natural history study performed on a large, newly diagnosed NF2 patient cohort with vestibular schwannomas showed rates of hearing decline of 5 % at 1 year, 13 % at 2 years, and 16 % at 3 years. Rates of radiographic tumor progression in this population were higher: 31 % at 1 year, 64 % at 2 years, and 79 % at 3 years (Plotkin et al. 2014). Any progression of symptoms such as hearing loss may be considered failure of conservative management. By contrast, large lesions >3 cm are approached with frontline surgery, and those with brainstem compression may require urgent surgical intervention (Blakeley et al. 2011).

Vestibular schwannoma surgery is challenging and often is performed by multidisciplinary teams of neurosurgeons and neuro-otologists. Several surgical approaches have been described including translabyrinthine, middle cranial fossa, and suboccipital, each with its own advantages and potential risks. Ipsilateral facial nerve damage has been reported in 17 % of patients undergoing removal of vestibular schwannomas greater than 2.5 cm (Grey et al. 1996). This complication can have significant impact on patient quality of life.

Recently, radiosurgery has become more popular in the management of vestibular schwannomas. The main goal of radiosurgery is tumor control, which appears to be decreased in the setting of NF2 as compared to patients with sporadic vestibular schwannomas. In one large retrospective single institutional series of NF2-associated vestibular schwannomas treated with radiosurgery, 8-year local control was 50 % and 3-year hearing preservation was 40 % (Rowe et al. 2008), though subsequent, smaller, series have reported more favorable tumor control outcomes (e.g., Mallory et al. 2014). While secondary malignancies and malignant transformation of vestibular schwannomas following radiosurgery are rare, the majority of described cases have been in the setting of preexisting NF2, suggesting that these patients are at an increased risk of radiation-induced cancer induction (Balasubramaniam et al. 2007).

The therapeutic landscape in NF2-associated lesions has recently been transformed by successes in early trials of targeted biologic therapies based on our evolving understanding of schwannoma biology and the signaling consequences of merlin loss. Schwannomas are known to express high levels of the pro-angiogenic signaling factor VEGF (Caye-Thomasen et al. 2003). In a pilot trial of the anti-VEGF antibody bevacizumab in ten NF2 patients with progressive vestibular schwannoma who were not candidates for standard therapy, six patients exhibited radiographic tumor responses, and four of seven hearing-evaluable patients had objective improvement in hearing (Plotkin and Stemmer-Rachamimov 2009). Similarly promising tumor and hearing response rates were seen in a larger bevacizumab-treated NF2 cohort with longer-term follow-up; however, continuous therapy was required for sustained responses (Plotkin et al. 2012). Unfortunately, in NF2-associated meningiomas, bevacizumab responses were transient and much less frequent, implicating signaling pathways other than VEGF in the growth of these entities (Nunes et al. 2013). Based on the finding that the EGFR signaling pathway was negatively regulated by NF2 (Curto et al. 2007), a recent phase II trial of the EGFR/ErbB2 inhibitor lapatinib in children and adults with NF2-associated vestibular schwannomas revealed volumetric responses in 24 % of patients and hearing responses in 31 % of patients with a median time to overall progression of 14 months (Karajannis et al. 2012). mTOR signaling was also shown to be dysregulated in preclinical models of NF2; however, a recent phase II study of the mTOR inhibitor everolimus in NF2-associated vestibular

schwannoma was negative (Karajannis et al. 2014). At this time, more clinical experience is warranted to better define the most effective treatment(s) and key criteria for initiating therapy. Multiple rationally informed clinical trials of a variety of targeted agents in NF2 including lapatinib, axitinib, everolimus, and bevacizumab are ongoing (Karajannis and Ferner 2015).

12.4 Tuberous Sclerosis Complex

12.4.1 Epidemiology

Tuberous sclerosis complex (TSC), previously known as Bourneville's disease, is an autosomal dominant disorder with a growing incidence currently estimated to be 1:6000 to 1:9000 due to improved diagnostic tests (Roach and Sparagana 2004). There is no race or gender predilection, and onset of symptoms varies from infancy to late childhood (Roach et al. 1998; Sparagana and Roach 2000).

12.4.2 Molecular Biology and Genetics

TSC is genetically heterogeneous with two implicated genes: TSC1 on chromosome 9q34 encodes hamartin, a 130 kDa tumor suppressor protein, and TSC2 on chromosome 16p13 encodes tuberin, a 200 kDa tumor suppressor protein. Both proteins form a ubiquitous intracellular complex called the TSC complex, which is involved in many cell regulatory processes.

Through the GTPase-activating function of tuberin, the TSC tumor suppressor complex drives the small GTPase, termed Ras homolog enhanced in brain (Rheb), into the inactive guanosine diphosphate-bound state. Rheb in the guanosine triphosphate-bound active state is a positive effector of *m*ammalian *t*arget *o*f *r*apamycin (mTOR). Mutations in either hamartin or tuberin drive Rheb into the guanosine triphosphate-bound state, which results in constitutive mTOR signaling. mTOR appears to mediate many of its effects on cell growth through the phosphorylation of the ribosomal protein S6 kinases (S6Ks) and the repressors of protein synthesis initiation factor eIF4E, the 4EBPs. The S6Ks act to increase cell growth and protein synthesis, whereas the 4EBPs serve to inhibit these processes. mTOR interacts with the S6Ks and 4EBPs through an associated protein, raptor.

Mutation of tuberin or hamartin leads to constitutive activation of mTOR, which results in the hamartomatous lesions in the brain, kidney, heart, lung, CNS, and other organs of the body. More aggressive tumors, such as angiomyolipomas, can also arise. Such mutations are commonly found in patients with TSC, but up to one third of clinically diagnosed patients have no discernable mutation (Jones et al. 2000). This might be in part due to somatic mosaicism. Reasons for the clinical variability associated with identical mutations remain elusive. Recent reports suggest that patients with mutations in *TSC1* gene are less severely affected than patients with mutations in the *TSC2* gene, a finding that provides some help when counseling parents (Jansen et al. 2008; van Eeghen et al. 2012).

12.4.3 Diagnostic Criteria and Clinical Features

TSC is characterized by seizures, behavioral problems, mental retardation, and development of benign tumors (hamartomas) in multiple organs. The classic TSC triad consists of seizures, mental retardation, and adenoma sebaceum (Hanno and Beck 1987; Curatolo 1996; Roach et al. 1998). Adenoma sebaceum are pathologically best characterized as facial angiofibromas. The CNS lesions seen with TSC include cortical tubers, subependymal nodules, and subependymal giant cell astrocytomas (SEGA). Cortical tubers present a hallmark for the disease. They form during development and represent a disorder of neural proliferation. Recently updated diagnostic guidelines rely upon molecular testing and a variety of clinical criteria to establish the diagnosis of TSC (Table 12.3). A definite diagnosis of TSC requires identification of a pathogenic mutation in TSC1 or TSC2 or a

Table 12.3 Diagnostic criteria for tuberous sclerosis (Northrup and Krueger 2013)

Genetic diagnostic criteria:	
The identification of either a TSC1 or TSC2 pathogenic mutation in DNA from normal tissue is sufficient to make a definite diagnosis of tuberous sclerosis complex (TSC). A pathogenic mutation is defined as a mutation that clearly inactivates the function of the TSC1 or TSC2 proteins (e.g., out-of-frame indel or nonsense mutation), prevents protein synthesis (e.g., large genomic deletion), or is a missense mutation whose effect on protein function has been established by functional assessment (www.lovd.nl/TSC1, www.lovd/TSC2, and Hoogeveen-Westerveld et al. 2012, 2013). Other TSC1 or TSC2 variants whose effect on function is less certain do not meet these criteria and are not sufficient to make a definite diagnosis of TSC. Note that 10–25 % of TSC patients have no mutation identified by conventional genetic testing, and a normal result does not exclude TSC or have any effect on the use of clinical diagnostic criteria to diagnose TSC	
Clinical diagnostic criteria:	
Major features	**Minor features**
1. Hypomelanotic macules (≥3, at least 5 mm diameter)	1. "Confetti" skin lesions
2. Angiofibroma (≥3) or fibrous cephalic plaque	2. Dental enamel pits (≥3)
3. Ungual fibromas (≥2)	3. Intraoral fibromas (≥2)
4. Shagreen patch	4. Retinal achromic patch
5. Multiple retinal hamartomas	5. Multiple renal cysts
6. Cortical dysplasias[a]	6. Nonrenal hamartomas
7. Subependymal nodules	
8. Subependymal giant cell astrocytoma	
9. Cardiac rhabdomyoma	
10. Lymphangioleiomyomatosis (LAM)[b]	
11. Angiomyolipomas (≥2)[b]	

Definite diagnosis: two major features or one major feature with ≥2 minor features. Possible diagnosis: either one major feature or ≥2 minor features

[a]Includes tubers and cerebral white matter radial migration lines

[b]A combination of the two major clinical features (LAM and lymphangioleiomyomatosis) without other features does not meet criteria for a definite diagnosis

combination of either two major features or one major feature and two minor features. For a probable diagnosis of TSC, one major feature or two or more minor features must be present.

Epilepsy is the most common neurological symptom associated with TSC, present in 60–90 % of cases, and often beginning in the first year of life (Jozwiak et al. 2000; Thiele 2004). In one analysis of 105 patients diagnosed with TSC, 47 % had abnormal cognitive function that was associated with refractory seizures and mutations in the *TSC2* gene (Winterkorn et al. 2007). Patients with tuberous sclerosis complex face a high risk of neuropsychiatric impairments: for example, the prevalence of autism spectrum disorders in TSC has recently been estimated to be as high as 25–50 % (de Vries et al. 2015).

Hypomelanotic lesions, ash-leaf macule depigmented nevi resembling vitiligo, may be noted at birth and can be seen in more than half of TSC patients before 2 years of age. These are best visualized with ultraviolet light (Wood lamp). Ash-leaf spots are seen in up to 90 % of patients with TSC. Facial angiofibromas (adenoma sebaceum) skin lesions consist of vascular and connective tissue elements. The red papular rash typically extends over the nose and down the nasolabial folds toward the chin, cheeks, and malar regions. Skin lesions gradually enlarge, manifesting ultimately in 90 or more percent of TSC patients (Northrup and Krueger 2013).

12.4.4 Natural History and Prognosis

The leading cause of morbidity and mortality in TSC patients is caused by neurologic manifestation of the disease followed by renal complications (Franz 2004). Refractory epilepsy is common and leads to poor cognitive outcome (Winterkorn et al.

2007). SEGAs can cause hydrocephalus and require surgical intervention (Cuccia et al. 2003). Additional abnormalities occur in the eyes, skin, kidneys, bones, heart, and lungs. Prognosis varies with the individual manifestations of the disease. Major causes of death in a large TSC Scottish cohort were renal disease, followed by brain tumors, pulmonary lymphangiomyomatosis, status epilepticus, and bronchopneumonia (Shepherd and Stephenson 1992). In severe cases, death occurs in the second decade of life (Curatolo 1996; Webb et al. 1996; Sparagana and Roach 2000).

12.4.5 Laboratory Studies

Molecular genetic testing has become available in clinical practice and may be helpful in young patients who are less than 2 years of age, since many of the clinical signs are not present until later in life. Recently updated consensus diagnostic criteria for TSC now include the identification of a pathogenic *TSC1* or *TSC2* mutation as sufficient for the formal diagnosis of tuberous sclerosis, independent of clinical findings (Table 12.3, Northrup and Krueger 2013). Various molecular assays reveal the presence of a mutation in 75–90% of cases (Northrup and Krueger 2013). According to recently updated TSC management guidelines, genetic testing is indicated for genetic counseling purposes or when the diagnosis of TS is suspected but cannot be clinically confirmed (Krueger and Northrup 2013).

12.4.6 Imaging Studies

In addition to the recent adoption of genetic testing to formally establish a diagnosis of TSC, clinical criteria are commonly used as detailed in Table 12.3.

Approximately 95% of patients with clinical features of TSC have abnormalities on CT scans (Menkes and Maria 2000). Typically, there are hypodense subependymal nodules lining the ventricles (Fig. 12.5a), usually calcified after the first year of life, and 50% of affected individuals demonstrate calcified cortical hamartomas. SEGAs located at or near the foramen of Monro enhance brightly following contrast administration. Calcified subependymal and cortical nodules are seen in 95% of individuals with TSC, leaving CT as a simpler diagnostic tool than MRI by obviating the need for general anesthesia in children (Braffman et al. 1990; Menor et al. 1992; Mukonoweshuro et al. 1999; Fischbein et al. 2000).

Brain MRI is preferable for defining the exact number and location of cerebral cortical and subcortical tubers, white matter lesions, and areas of heterotopias (Braffman et al. 1990; Menor et al. 1992; Mukonoweshuro et al. 2001; Fischbein et al. 2000). Tubers or sclerotic white patches involving the gyri or white matter occur mostly in the cerebrum, while cerebellar, brainstem, and spinal cord lesions occur less commonly. Cortical tubers and hamartomas change in appearance as the brain myelinates. They are initially hyperintense on T1-weighted images and hypointense on T2-weighted images, but as brain myelination progresses, this imaging pattern reverses. White matter lesions appear as hyperintense linear bands in cerebrum and cerebellum. In infants, bands are hypointense to unmyelinated white matter on T2-weighted images and are hyperintense to white matter in older children and adults (Fig. 12.5b). SEGAs at or near foramen of Monro display intense postcontrast enhancement, although the pattern can be heterogeneous (Fig. 12.5c). MR spectroscopy can be useful to distinguish them from cortical tubers.

Refinement of MRI techniques and interpretation to identify the location of epileptogenic lesions in TS patients remains an area of active research (Jahodova et al. 2014; Gallagher et al. 2009, 2010; Peters et al. 2013). PET/MRI fusion imaging has been studied to identify epileptogenic tubers with great promise for improving surgical cure rates for intractable epilepsy (Chandra et al. 2006).

12.4.7 Treatment

TSC affects multiple organs, and treatment recommendations vary according to each specific organ manifestation. Recently developed consensus surveillance and management guide-

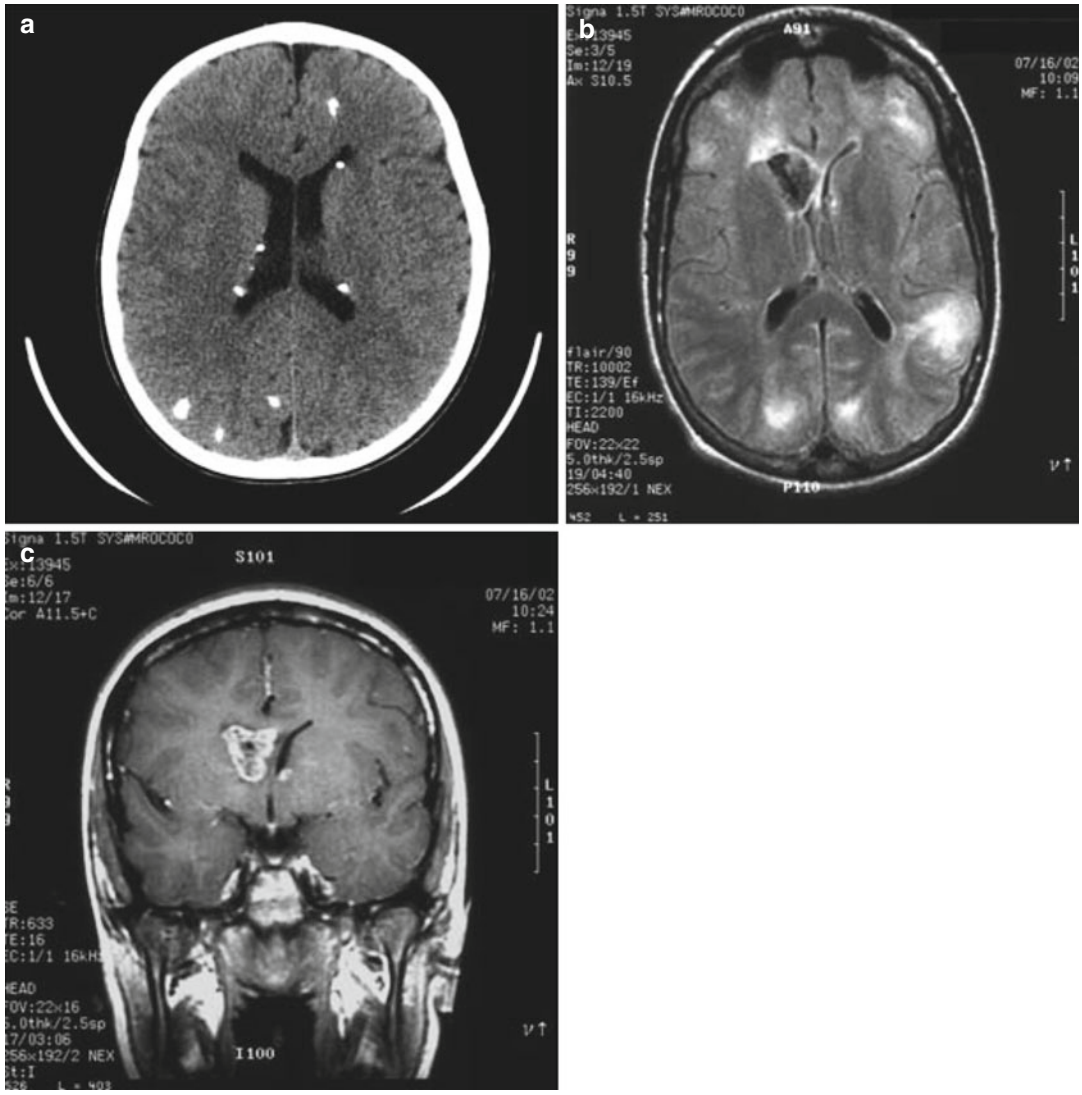

Fig. 12.5 Tuberous sclerosis complex. (**a**) Axial CT image of multiple calcified subependymal nodules. Other calcifications are also seen within the cortex. (**b**) Bilateral cortical tubers of varying sizes and a frontal subependymal giant cell astrocytoma (SEGA) are seen on this T2-weighted image. (**c**) A postcontrast T1-weighted coronal image from the same patient demonstrates the proximity of the tumor to the foramen of Monro

lines for TSC patients provide detailed recommendations for diagnosis, surveillance, and treatment of organ site-specific manifestations of TSC (Krueger and Northrup 2013). For diagnosis of CNS abnormalities, all TSC patients are recommended to have an initial MRI of the brain with and without gadolinium contrast to identify tubers, subependymal nodules, and subependymal giant cell astrocytomas. CT or cranial ultrasound are second-line diagnostic modalities. All pediatric patients are recommended to undergo a baseline EEG even in the absence of seizures. A baseline neuropsychiatric assessment and referral for specialized management is also strongly recommended in view of the risk of significant neuropsychiatric manifestations in TSC.

Neurologically asymptomatic patients with TSC should undergo neuroimaging surveillance every 1–3 years until the age of 25 and, if SEGAs are present, continuing into adulthood. Updated

treatment recommendations for TSC-associated SEGA have recently been published (Roth et al. 2013). Surgical resection is recommended for acutely symptomatic SEGAs, while growing or asymptomatic SEGAs can be managed by surgical resection or medical therapy with mTOR inhibitors. The efficacy of mTOR inhibition with everolimus in shrinking or stabilizing TS-associated SEGAs has been demonstrated in a randomized phase III trial (Franz et al. 2013) and has revolutionized the management paradigm for such patients. Early results (e.g., Krueger et al. 2010) suggest that mTOR inhibition may reduce seizure frequency in some TS patients; however, the efficacy of this approach awaits larger-scale prospective verification. Everolimus has also been shown to be efficacious in reducing the volume of renal angiomyolipomas in TS patients (Bissler et al. 2013).

Treatment and surveillance recommendations for extracranial manifestations of TS have also been updated at the 2012 International Tuberous Sclerosis Consensus Conference (Krueger and Northrup 2013). An organ site-specific summary of recommendations for newly diagnosed and established tuberous sclerosis patients is provided in Table 12.4.

12.5 Ataxia Telangiectasia

12.5.1 Epidemiology

Ataxia telangiectasia (AT) is an autosomal recessive disorder with an incidence of 1:40,000 to 1:80,000 and equal predilection in both sexes. Patients with AT may present during infancy with ataxia without any cutaneous manifestations, which may become apparent after 2 years of age (Gosink et al. 1999; Lavin 1999).

12.5.2 Molecular Biology and Genetics

The gene for AT has been mapped to the long arm of chromosome 11 (11q23.3). The ataxia telangiectasia mutated (*ATM*) gene is very large with 66 exons spanning 150 kb of the genome, which renders mutation analysis challenging (Bakkenist and Kastan 2003). The *ATM* gene product is a member of the phosphatidylinositol 3-kinase (PI3-kinase) family and is activated by autophosphorylation in response to DNA double-strand breaks, as well as by direct ATM protein oxidation (Guo et al. 2010) and by membrane receptors such as PDGFRβ (Kim et al. 2010). It contains a PI3-kinase domain, a putative leucine zipper, and a proline-rich region. The ATM protein detects DNA double-strand breaks and activates a number of substrates including p53, chk-2, nibrin, BRCA1, and TSC2, the latter serving to downregulate mTOR signaling (Ambrose and Gattia 2013; Kastan and Lim 2000; Shiloh 2003). ATM plays an important role in cellular responses to DNA damage, cell cycle control, and maintenance of telomere length and has recently been shown to be important for mitochondrial homeostasis (Ambrose et al. 2007; Eaton and Lin 2007). Additional roles of ATM outside of DNA repair, such as in regulation of synaptic vesicle trafficking and in epigenetics, are emerging and may be critical to fully understanding the neurodegenerative phenotype of its deficiency in humans (Herrup 2014).

Over 400 different mutations have been identified in AT patients. Database screening has revealed that most mutations are unique to a given family. Mutations are distributed anywhere in the gene, and no hotspots or high-frequency mutations have been reported (Concannon and Gatti 1997; Mitui et al. 2003). Approximately 90 % of mutations are of the frameshift or premature truncation type, making the majority null mutations. Missense mutations occur in 10 % of the known mutations among AT families (Chun and Gatti 2004; Nakamura et al. 2014). Increased variant protein expression and residual kinase activity have been shown to correlate with a milder phenotype and increased life expectancy in AT patients (Staples and McDermott 2008; Micol et al. 2011; Verhagen et al. 2011).

Table 12.4 Surveillance and management recommendations for newly diagnosed or suspected tuberous sclerosis complex (TSC)

Organ system or specialty area	Recommendation
Genetics	Obtain three-generation family history to assess for additional family members at risk of TSC
	Offer genetic testing for family counseling or when TSC diagnosis is in question but cannot be clinically confirmed
	Offer genetic testing and family counseling, if not done previously, in individuals of reproductive age or newly considering having children
Brain	Perform magnetic resonance imaging (MRI) of the brain to assess for the presence of tubers, subependymal nodules (SEN), migrational defects, and subependymal giant cell astrocytoma (SEGA)
	Evaluate for TSC-associated neuropsychiatric disorder (TAND)
	During infancy, educate parents to recognize infantile spasms, even if none have occurred at the time of first diagnosis
	Obtain baseline routine electroencephalogram (EEG). If abnormal, especially if features of TAND are also present, follow up with a 24-h video EEG to assess for subclinical seizure activity
	Obtain magnetic resonance imaging (MRI) of the brain every 1–3 years in asymptomatic TSC patients younger than age 25 years to monitor for new occurrence of subependymal giant cell astrocytoma (SEGA). Patients with large or growing SEGA, or with SEGA causing ventricular enlargement but yet are still asymptomatic, should undergo MRI scans more frequently, and the patients and their families should be educated regarding the potential of new symptoms. Patients with asymptomatic SEGA in childhood should continue to be imaged periodically as adults to ensure there is no growth
	Surgical resection should be performed for acutely symptomatic SEGA. Cerebral spinal fluid diversion (shunt) may also be necessary. Either surgical resection or medical treatment with mammalian target of rapamycin complex (mTOR) inhibitors may be used for growing but otherwise asymptomatic SEGA. In determining the best treatment option, discussion of the complication risks, adverse effects, cost, length of treatment, and potential impact on TSC-associated comorbidities should be included in the decision-making process
	Perform screening for TSC-associated neuropsychiatric disorders (TAND) features at least annually at each clinical visit. Perform comprehensive formal evaluation for TAND at key developmental time points: infancy (0–3 years), preschool (3–6 years), pre-middle school (6–9 years), adolescence (12–16 years), early adulthood (18–25 years), and as needed thereafter. Management strategies should be based on the TAND profile of each patient and should be based on evidence-based good practice guidelines/practice parameters for individual disorders (e.g., autism spectrum disorder, attention deficit hyperactivity disorder, anxiety disorder). Always consider the need for an individual educational program (IEP). Sudden change in behavior should prompt medical/clinical evaluation to look at potential medical causes (e.g., SEGA, seizures, renal disease)
	Obtain routine electroencephalograph (EEG) in individuals with known or suspected seizure activity. The frequency of routine EEG should be determined by clinical need rather than a specific defined interval. Prolonged video EEG, 24 h or longer, is appropriate when seizure occurrence is unclear or when unexplained sleep, behavioral changes, or other alteration in cognitive or neurological function is present
	Vigabatrin is the recommended first-line therapy for infantile spasms. Adrenocorticotropin hormone (ACTH) can be used if treatment with vigabatrin is unsuccessful. Anticonvulsant therapy of other seizure types in TSC should generally follow that of other epilepsies. Epilepsy surgery should be considered for medically refractory TSC patients, but special consideration should be given to children at younger ages experiencing neurological regression and is best if performed at epilepsy centers with experience and expertise in TSC

(continued)

Table 12.4 (continued)

Organ system or specialty area	Recommendation
Kidney	Obtain MRI of the abdomen to assess for the presence of angiomyolipoma and renal cysts
	Screen for hypertension by obtaining an accurate blood pressure
	Evaluate renal function by determination of glomerular filtration rate (GFR)
	Obtain MRI of the abdomen to assess for the progression of angiomyolipoma and renal cystic disease every 1–3 years throughout the lifetime of the patient
	Assess renal function (including determination of glomerular filtration rate (GFR)) and blood pressure at least annually
	Embolization followed by corticosteroids is first-line therapy for angiomyolipoma presenting with acute hemorrhage. Nephrectomy is to be avoided. For asymptomatic, growing angiomyolipoma measuring larger than 3 cm in diameter, treatment with an mTOR inhibitor is the recommended first-line therapy. Selective embolization or kidney-sparing resection is acceptable second-line therapy for asymptomatic angiomyolipoma
Lung	Perform baseline pulmonary function testing (pulmonary function testing and 6-min walk test) and high-resolution chest computed tomography (HRCT), even if asymptomatic, in patients at risk of developing lymphangioleiomyomatosis (LAM), typically females 18 years or older. Adult males, if symptomatic, should also undergo testing
	Provide counsel on smoking risks and estrogen use in adolescent and adult females
	Perform clinical screening for lymphangioleiomyomatosis (LAM) symptoms, including exertional dyspnea and shortness of breath, at each clinic visit. Counseling regarding smoking risk and estrogen use should be reviewed at each clinic visit for individuals at risk of LAM
	Obtain high-resolution computed tomography (HRCT) every 5–10 year in asymptomatic individuals at risk of LAM if there is no evidence of lung cysts on their baseline HRCT. Individuals with lung cysts detected on HRCT should have annual pulmonary function testing (pulmonary function testing and 6-min walk) and HRCT interval reduced to every 2–3 years
	mTOR inhibitors may be used to treat LAM patients with moderate to severe lung disease or rapid progression. TSC patients with LAM are candidates for lung transplantation, but TSC comorbidities may impact transplant suitability
Skin	Perform a detailed clinical dermatologic inspection/exam
	Perform a detailed clinical dermatologic inspection/exam annually
	Rapidly changing, disfiguring, or symptomatic TSC-associated skin lesions should be treated as appropriate for the lesion and clinical context, using approaches such as surgical excision, laser(s), or possibly topical mTOR inhibitor

Teeth	Perform a detailed clinical dental inspection/exam
	Perform a detailed clinical dental inspection/exam at minimum every 6 months and panoramic radiographs by age 7 years, if not performed previously
	Symptomatic or deforming dental lesions, oral fibromas, and bony jaw lesions should be treated with surgical excision or curettage when present
Heart	Consider fetal echocardiography to detect individuals with high risk of heart failure after delivery when rhabdomyomas are identified via prenatal ultrasound
	Obtain an echocardiogram in pediatric patients, especially if younger than 3 years of age
	Obtain an electrocardiogram (ECG) in all ages to assess for underlying conduction defects
	Obtain an echocardiogram every 1–3 years in asymptomatic pediatric patients until regression of cardiac rhabdomyomas is documented. More frequent or advanced diagnostic assessment may be required for symptomatic patients
	Obtain electrocardiogram (ECG) every 3–5 years in asymptomatic patients of all ages to monitor for conduction defects. More frequent or advanced diagnostic assessment such as ambulatory and event monitoring may be required for symptomatic patients
Eye	Perform a complete ophthalmologic evaluation, including dilated funduscopy, to assess for retinal lesions and visual field deficits
	Perform annual ophthalmologic evaluation in patients with previously identified ophthalmologic lesions or vision symptoms at the baseline evaluation. More frequent assessment, including those treated with vigabatrin, is of limited benefit and not recommended unless new clinical concerns arise

12.5.3 Diagnostic Criteria and Clinical Features

AT is the most common ataxia in infancy (Kamiya et al. 2001), although the initial manifestations of cerebellar ataxia may not be noted until early walking. AT is a common cause of progressive ataxia in children younger than 10 years of age, second only to tumors of the posterior fossa. Ataxia is generally the presenting symptom of AT. Oculomotor apraxia is a distinguishing feature of the disease, which is often present prior to the cutaneous findings.

Telangiectasias are a second major clinical manifestation of the disease (Table 12.5). Progressive oculocutaneous telangiectasias represent a key feature of AT. Bulbar conjunctivae telangiectasias first appear between 2 and 8 years of age and subsequently involve the ears, eyelids, malar prominences, neck, antecubital and popliteal fossae, as well as dorsum of hands and palate. Initially they appear as bright-red, thick, symmetrical streaks that resemble atypical conjunctivitis and only later become frank telangiectasias. These skin lesions become more prominent with sunlight exposure and age. Premature aging of hair and skin is frequent.

Patients with AT have a high tendency to develop chronic sinopulmonary infections. The immunodeficiency involves both cellular and humoral immunities. Absence of the tonsils, adenoids, lymphoid tissue, and thymus gland is commonly seen in AT. The incidence of cancer in AT is approximately 100-fold higher than in matched populations. These neoplasms consist of non-Hodgkin's lymphoma, leukemia, and other solid tumors.

Table 12.5 Clinical features for ataxia telangiectasia (Menkes and Maria 2000)

Clinical features
Slowly progressive cerebellar ataxia
Choreoathetosis
Telangiectasia of the skin and conjunctiva
Susceptibility to sinobronchopulmonary infections
Cancer (non-Hodgkin's lymphoma, leukemias, solid tumors)

12.5.4 Natural History and Prognosis

Neurologic deterioration is progressive, and by the end of the first decade of life, children are confined to wheelchairs with myoclonic jerks, drooling, choreoathetosis, oculomotor abnormalities, and dysarthric speech (Paller 1987). Eighty-five percent of AT patients develop choreoathetosis, apraxia of eye movements, and nystagmus. The progressive cerebellar neurodegeneration is the most debilitating feature of AT. Over time patients also develop peripheral neuropathy and eventually spinal muscular atrophy. Intelligence is usually normal in young children but deteriorates with disease progression (Menkes and Maria 2000).

Growth retardation occurs in 72 % of patients with AT. Progeric changes have been noted in almost 90 % of AT patients with early loss of subcutaneous fat, loss of skin elasticity, and premature graying of hair by adolescence (Paller 1987). AT patients are immunodeficient with compromised humoral immune surveillance and cellular immunity. Specifically, AT patients have IgA deficiencies that predispose them to infectious agents that enter through exposed sites. Consequently, they tend to suffer recurrent bacterial and viral sinopulmonary infections that can be life-threatening (Paller 1987). Molecular mechanisms underlying this immunodeficient phenotype are gradually being unraveled (Jiang et al. 2015).

Children with AT have an increased incidence of cancer, primarily lymphoid tumors, due to acute sensitivity to ionizing radiation and defective cell cycle checkpoints (Kamiya et al. 2001). AT patients are 40–100 times more likely to develop leukemias, lymphomas, lymphosarcomas, and Hodgkin's disease, leading to neoplastic development in 30 % of patients. Lymphoreticular malignancies predominate in younger patients, whereas epithelial malignancies occur most frequently in adult patients (Suarez and Mahlaoui 2015; Paller 1987). Not surprisingly, death frequently occurs in late childhood or early teenage years. Mean age of death is 14 years (Kamiya et al. 2001) due to malignancy or complications from pulmonary infection and respiratory insufficiency.

A milder, adult-onset "variant" phenotype of AT has also been described, frequently presenting with extrapyramidal signs and more gradual or delayed development of ataxia (Saunders-Pullman et al. 2012; Verhagen et al. 2009). These patients may have a longer life span compared with individuals with classic AT, but remain at elevated risk for malignancy relative to the unaffected general population.

Some penetrance appears in AT heterozygotes leading to intermediate radiosensitivity and increased risk of cancer, particularly breast cancer. ATM heterozygotes have a ninefold increased risk of developing breast cancer, characterized by bilateral disease and early age of onset (Lavin et al. 1999).

12.5.5 Laboratory Studies

Highly elevated serum α-fetoprotein is detected in nearly 95 % of AT cases, and this laboratory marker often precedes the appearance of telangiectasias by several years (Menkes and Maria 2000). Patients with variant AT may have normal or more mildly elevated AFP levels (Saunders-Pullman et al. 2012).

AT patients may also display elevated levels of carcinoembryonic antigen (CEA) and low or absent total IgA or IgE levels. Markedly decreased serum IgA (<80 mg/L) and IgE (<3 mg/L) levels are seen in 70–90 % of AT patients. Conversely, IgM, IgG1, and IgG3 levels tend to be high (Menkes and Maria 2000). Elevated hepatic transaminases are seen in 40–50 % of patients, and glucose intolerance is seen in 50 % of patients. An unusual form of adolescent diabetes is observed in which hyperglycemia occurs with rare glycosuria, absent ketosis, insulin hypersecretion, and peripheral insulin resistance.

Chromosomal abnormalities occur 2–18 times more frequently in AT patients than in normal individuals, with chromosomal abnormalities observed in 80 % of AT patients. Rearrangements of chromosomes 7 and 14, and especially 14:14 translocations may anticipate the development of lymphoreticular malignancies (Lavin et al. 1999). Analysis of amniotic fluid allows prenatal diagnosis using measurements of α-fetoprotein and high-resolution chromosomal analysis. Diagnosis of AT may be confirmed by sequencing of the ATM locus in patients with clinical features of the syndrome and supported by cytogenetic studies showing chromosomal rearrangements and x-irradiation hypersensitivity of lymphocytes or fibroblasts derived from the patient.

12.5.6 Imaging Studies

MRI of the brain is normal with a well-formed cerebellum for many years after onset of ataxia. By 10 years of age, volume loss of the cerebellum often becomes apparent. Posterior fossa abnormalities include cerebellar atrophy, particularly of the anterior vermis, atrophy of the dentate, and atrophy of the olivary nuclei; spine MRI demonstrates degeneration of the posterior columns. These imaging findings correlate with well-described neuropathologic features of AT (Sahama et al. 2014a). In the cerebellum, there is a reduction in Purkinje cell number and atrophy of dentate nuclei. In addition, there is atrophy of anterior horn cells, demyelination of gracile fasciculi in the spinal cord, and appearance of nucleocytomegalic cells in the anterior pituitary. Preliminary studies with diffusion-weighted MRI techniques in AT patients have revealed signs of compromise in key cerebellar–corticomotor pathways, consistent with the ataxic phenotype (Sahama et al. 2014b). Cerebrovascular abnormalities can be noted on MRI in later stages of the disease (Habek et al. 2008).

12.5.7 Treatment

To date, there is no therapy available to cure or prevent progress of the disease, and interventions are mainly supportive. These efforts include prophylactic therapy for infections. Antibiotics and plasma gamma globulin infusions have been utilized for IgA deficiencies and intercurrent sinopulmonary infections. Thymus gland and bone

marrow transplantations have been reported as well. Judicious use of sunscreen is warranted to retard actinic-like skin progeric changes. Radiation therapy and radiomimetic chemotherapeutic agents should be avoided in treating lymphoreticular malignancies. Early pulmonary physiotherapy and physical therapy appropriate for the neurologic dysfunction should be instituted. Many treatments employed for ataxia, including acetylcholine, γ-aminobutyric acid, dopamine, diazepam, chlordiazepoxide, trihexyphenidyl, diphenhydramine, and haloperidol, have been ineffective, although a recent small study using amantadine sulfate has reported promising symptom response rates (Nissenkorn et al. 2013). A patient disabled with an extremely severe involuntary movement disorder responded well to dantrolene, a hydantoin compound. Corticosteroids have been shown to induce an alternate splice site in ATM expression and partially rescue the gene product's activity (Menotta et al. 2012). In small studies steroid preparations appear to mitigate and possibly delay symptom progression (Chessa et al. 2014). Neoplastic processes that require aggressive treatment with chemotherapy or radiation present a formidable challenge, given the high vulnerability to further oncologic insults in AT patients.

12.6 Von Hippel–Lindau Syndrome

12.6.1 Epidemiology

VHL is an autosomal dominant disorder with an incidence of 1:40,000 (Maher and Kaelin 1997). It exhibits 90% penetrance and equal incidence in males and females. Generally, VHL does not present during childhood, but more often during the second or third decade of life (Singh et al. 2001). Approximately 20% of cases are attributable to de novo mutations (Schmid et al. 2014).

12.6.2 Molecular Biology and Cytogenetics

The *VHL* gene maps to chromosome 3p25–p26 and is a putative tumor suppressor gene (Latif et al. 1993). Two VHL gene products have been identified that are translated from mRNAs generated from two alternative start codons. In most functional studies these two proteins are indistinguishable and, therefore, are referred to as one. The VHL protein (pVHL) lacks known enzymatic activity and instead is thought to function as a molecular adaptor in a variety of mechanistic roles (Frew and Krek 2008). Its most thoroughly understood role is in the oxygen-dependent ubiquitination for subsequent proteolytic degradation of the HIFα transcription factor family (Maxwell et al. 1999). These transcription factors control a variety of downstream pathways involved in cellular proliferation, angiogenesis, tumor invasion, and metastasis. HIFα-dependent signaling elements such as VEGF, PDGF, and TGFα have been implicated in VHL-associated neoplasia (Shen and Kaelin 2013). Recent findings have suggested that pVHL also modulates multiple HIFα-independent regulatory elements including NF-κB, p53, JunB, and others, which may also contribute to organ-specific tumorigenesis in the setting of VHL loss (Frew and Krek 2008).

For VHL, disease genotype–phenotype correlation has revealed a strong association of missense mutations with the presentation of pheochromocytoma (VHL Type 2), whereas null mutations carry a very low risk to develop these tumors (VHL Type 1) (Crossey et al. 1994; Chen et al. 1995). An extensive analysis of the VHL mutational spectrum in 945 families afflicted with the disorder has recently been published, revealing 1548 individual mutations of which approximately half were missense (Nordstrom-O'Brien et al. 2010).

12.6.3 Diagnostic Criteria and Clinical Features

Although it is classified as a neurocutaneous syndrome, VHL is not associated with any specific cutaneous lesion. VHL is a multisystem disorder with marked phenotypic variability (Table 12.6). The main pathological lesions are capillary hemangioblastomas that are highly vascularized benign tumors composed of pericytes and blood vessels. Patients with VHL are at risk of develop-

Table 12.6 Clinical features for von Hippel–Lindau

Clinical features
Cerebellar, retinal, and spinal cord hemangioblastoma
Renal cell carcinoma
Pheochromocytoma
Pancreatic neuroendocrine tumors
Pancreatic and renal cysts
Endolymphatic sac tumors
Polycythemia

ing benign and malignant tumors in the CNS, kidneys, retina, adrenal glands, pancreas, and reproductive adnexal organs. Retinal hemangioblastoma is often the first clinical sign and leads to diagnosis in 30 % of VHL patients (Joerger et al. 2005). Diagnostic features include a positive family history of VHL, identification of one CNS hemangioblastoma, or a single visceral lesion (Richard et al. 2000; Sims 2001). For example, a retinal or cerebellar hemangioblastoma, renal cell carcinoma, or pheochromocytoma in an at-risk individual would be an adequate criterion. In isolated cases with absent family histories, two or more retinal or cerebellar hemangioblastomas or a single hemangioblastoma and a visceral tumor are required for diagnosis. Multiple, frequent retinal angiomas may lead to retinal detachment, hemorrhage, and blindness if left untreated.

CNS hemangioblastomas occur most commonly in the cerebellum (44–72 %) and with a much lower incidence in the spinal cord (13–44 %) at a mean age of 33 years (Wanebo et al. 2003). These lesions are often multiple and are generally benign without metastases. Surgical excision results in excellent clinical outcome. Mean age of onset of cerebellar hemangioblastomas in VHL is considerably younger than in sporadic cases (Richard et al. 2000; Sims 2001). Cerebellar hemangioblastomas are found in approximately 75 % of patients with VHL. However, only 5–30 % of all patients with cerebellar hemangioblastomas are found to have VHL. Many patients with VHL ultimately develop multiple CNS hemangioblastomas, and management of brainstem and spinal tumors can be difficult. Thus, CNS involvement remains an important cause of morbidity and mortality in VHL patients.

Fifty to 70 % of VHL patients develop renal cysts, although renal impairment from cysts is rare. However, the lifetime risk of clear cell renal cell carcinoma is greater than 70 %, and renal cell carcinoma is a major cause of death in VHL patients. Pheochromocytomas arise in up to 24 % of patients with VHL, with a mean age of 27 years at presentation (Joerger et al. 2005). These tumors may be multiple, bilateral, or extra-adrenal. Pancreatic neuroendocrine tumors develop in 5–17 % of patients with VHL, with a mean age of 36 years at presentation (Hes et al. 2001a, b). Locally aggressive endolymphatic sac tumors arising from the posterior aspect of the temporal bone and leading to hearing loss and vestibular dysfunction have also been reported in association with VHL (Kim et al. 2013).

12.6.4 Natural History and Prognosis

Patients with VHL usually present in adulthood. Initial symptoms are often visual and related to retinal angiomas with a mean age of onset of 20–40 years. Symptoms from cerebellar hemangioblastomas present later and include headache, disequilibrium, nausea, and vomiting. In a large 10-year retrospective NIH study of 160 consecutive VHL patients, many patients presented with mass effect attributable to a cyst that was far greater in size than the causative tumor (Wanebo et al. 2003). Neither tumors nor cysts spontaneously diminished in size although many untreated tumors remained the same size for several years. The tumors demonstrated a stepwise pattern of growth with enlargement followed by a plateau. Usually the mass effect caused by the cyst was responsible for symptoms. Similar findings were recently reported in a large prospective natural history study of VHL-related hemangioblastomas in 225 patients carried out by the same group (Lonser et al. 2014).

The median age of death for patients with VHL is approximately 50 years (Wilding et al. 2012). Clear cell variant renal cell carcinomas and CNS hemangioblastomas are the leading

causes of VHL-related mortality (Maher et al. 1990; Singh et al. 2001).

12.6.5 Laboratory Studies

Laboratory studies are very nonspecific. Urinary catecholamines, VMA, and HVA may be elevated in cases of pheochromocytoma, with VHL-associated pheochromocytomas associated with solitary elevations in normetanephrine (Eisenhofer et al. 2011). Hemangioblastomas may produce excess erythropoietin resulting in elevated hematocrit values. Commercial genetic testing is now available with sequencing of the VHL gene.

12.6.6 Imaging Studies

With CT head scanning, a low-density cystic mass is often present in the posterior fossa. Isodense mural nodules may enhance intensely with contrast (Fischbein et al. 2000). On MRI, brain cysts may be isointense to cerebrospinal fluid or proteinaceous (hyperintense on T1-weighted sequences) with variable hyper- or hypointensity on T2-weighted sequences (Fig. 12.6). Prominent flow voids are seen in and adjacent to solid portions of the hemangioblastoma. Conventional catheter angiography demonstrates intense tumor blush localized to the posterior fossa. The typical blood supply is from superior cerebellar, anterior inferior cerebellar, or posterior inferior cerebellar arteries but may also arise from branches of the internal and external carotid arteries. Angiography may assist with operative planning, and, if possible, embolization may reduce the tumor vascularity allowing resection with reduced blood loss. Brain MRI with thin slice sequences through the temporal bone is the diagnostic paradigm of choice for imaging endolymphatic sac tumors in VHL patients. Abdominal MRI is recommended to characterize and follow VHL-associated renal and pancreatic abnormalities, while pheochromocytomas in patients with elevated catecholamines are localized using CT/MRI in addition to MIBG and/or DOPA-PET nuclear medicine studies (Schmid et al. 2014).

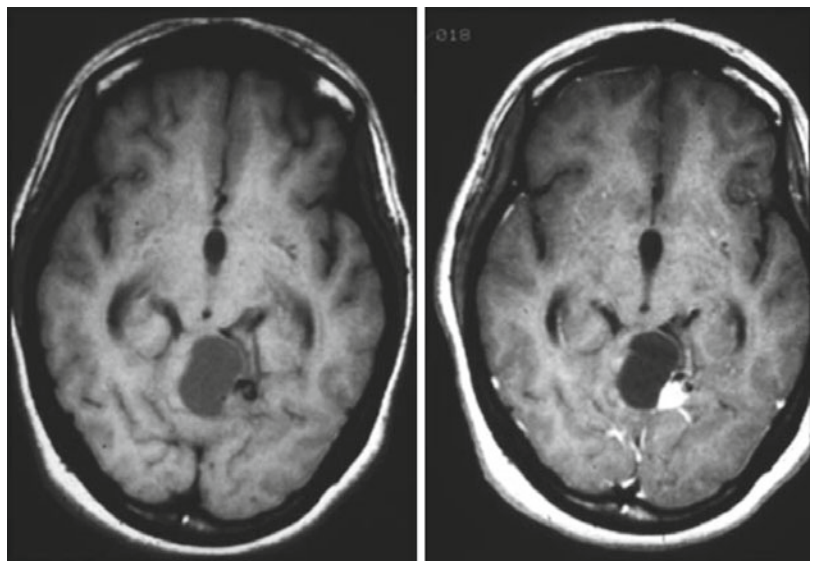

Fig. 12.6 VHL syndrome. T1-weighted images, pre- and postcontrast, demonstrating a small enhancing tumor nodule adjacent to a cyst located within the cerebellar vermis. The cyst contents are slightly hyperintense to cerebrospinal fluid

12.6.7 Treatment

To identify retinal angiomas, ophthalmologic examinations are required, and, when indicated, laser therapy and cryotherapy are effective (Hes et al. 2001a, b). Surgical removal of symptomatic lesions may also be considered. The NIH group emphasizes that the pattern of growth may be variable and saltatory growth is common (Wanebo et al. 2003; Lonser et al. 2014). Some tumors remain quiescent for many years, while others grow quickly over several months. As aforementioned, the growth of the cyst is often greater than the tumor itself and is responsible for the development of symptoms related to mass effect. In their series, asymptomatic patients rarely underwent surgery. Overall, surgical resection of cerebellar and even brainstem and spinal cord tumors was associated with acceptable morbidity and is considered first-line therapy (Capitanio et al. 2013). External beam radiation or stereotactic radiosurgery may be helpful for multiple or inaccessible lesions. One group reported radiosurgical hemangioblastoma local control rates of ~80 % at 5 years and ~50 % at 15 years (Asthagiri et al. 2010), while outcomes recently reported by an international consortium were somewhat more favorable (Kano et al. 2015). Infratentorial craniospinal radiation for patients with diffuse hemangioblastomas in the posterior fossa and spinal canal has also been described in a small pilot study, with good treatment tolerance and evidence of disease stabilization in a subset of patients (Simone et al. 2011). Antiangiogenic agents and multi-kinase inhibitors have been investigated as salvage therapies for progressive hemangioblastoma in VHL with evidence of measurable but limited benefit in a number of case reports and small trials with larger trials ongoing (Capitanio et al. 2013). Based on preliminary reports, retinal hemangioblastomas may exhibit favorable responses following administration of the anti-VEGF monoclonal antibody bevacizumab.

Renal cell carcinomas in VHL have very low metastatic potential at sizes <3 cm and may be managed with active surveillance using serial MRI until this size threshold is approached. Definitive management is primarily with nephron-sparing surgery if feasible given tumor burden, with the goal of minimizing the overall number of surgical procedures to best preserve renal function. Percutaneous CT-guided RFA may have a role in the nonsurgical treatment of smaller RCCs.

Pheochromocytomas in VHL are managed similarly to sporadic lesions, with frontline laparoscopic adrenalectomy after appropriate preoperative alpha-adrenergic blockade. It is important to exclude pheochromocytoma before performing any other surgical intervention in VHL patients due to the risk of pheochromocytoma-associated perioperative complications (Schmid et al. 2014).

Localized pancreatic neuroendocrine tumors in VHL are managed surgically. An increased risk of metastasis has been found for lesions >3 cm and a tumor doubling time of <500 days. Metastatic potential may also be increased in patients with a VHL exon 3 mutation (Blansfield et al. 2007; Corcos et al. 2008).

Multiple angiogenesis and multi-kinase inhibitors have shown efficacy in large prospective studies of metastatic clear cell renal cell carcinoma (ccRCC) in the non-VHL population. Given that pVHL mutation or loss is implicated as a central driving event in both sporadic and syndromic ccRCC, metastatic lesions in VHL patients are managed similarly to those in whom ccRCC occurs sporadically. Based on recent data, frontline agents may include one of sunitinib, pazopanib, bevacizumab plus interferon, and temsirolimus, while second-line therapies include everolimus, axitinib, and sorafenib (Sun et al. 2013; Coppin and Kollmannsberger 2011; Motzer et al. 2013). Data specific to VHL patients are more limited given the rarity of the syndrome, but a pilot trial of sunitinib in VHL patients revealed shrinkage of RCC with no overt responses in other lesion types (Jonasch et al. 2011).

Surveillance guidelines recommend screening patients with VHL annually or even biannually with MRI of the brain and spine. High-resolution

MRI scans through the temporal bones are recommended to screen for endolymphatic sac tumors. Annual fundoscopic exams are recommended starting at 6 years of age. Abdominal MRI scans, CT scans, or ultrasounds should be performed at least once per year starting at 15–18 years of age. To assess for pheochromocytoma, annual plasma and/or urine catecholamines/metanephrines should be checked (Schmid et al. 2014; Maher et al. 2011; Joerger et al. 2005).

12.7 Sturge–Weber Syndrome

12.7.1 Epidemiology

SWS, or encephalofacial angiomatosis, is a rare, sporadic neurocutaneous syndrome. The incidence is currently estimated to be 1:50,000. There is no sexual predilection and no racial bias. Although there are rare familial cases of SWS, there are no convincing data to suggest that it is a heritable condition in the majority of afflicted patients. Indeed, recent data suggest that the syndrome is associated with a postzygotic, somatic, mosaic mutation in the *GNAQ* locus (Shirley et al. 2013).

12.7.2 Genetic and Molecular Biology

Up until 2013, little was known regarding the genetic determinants of SWS. Whole-exome sequencing of DNA from normal and visibly affected tissue in three SWS patients revealed the presence of an activating mutation (p.Arg183Gln) in the *GNAQ* locus on chromosome 9q21, which encodes for a Gα-protein adaptor that mediates signaling between GPCRs and downstream effectors. The mutation was identified in affected tissue samples among 88% (23/26) of participants with SWS and in 92% (12/13) of samples obtained from port-wine stains (nevi flammei) in patients with no apparent SWS. The mutation was not found in six samples from control patients and in four samples of unrelated cerebrovascular malformations. It was hypothesized that severity of the resultant phenotype, from isolated port-wine stain to full SWS, depended on the timing of the mutational event during development (Shirley et al. 2013). From a pathologic perspective, malformations of embryonic vascular plexi give rise to abnormalities of the skin, leptomeninges, choroids, and cortex. Interference with vascular drainage at 5–8 weeks of gestation affects the face, eye, leptomeninges, and brain (Taly et al. 1987; Maiuri et al. 1989). Resultant angiomatosis is accompanied by poor superficial cortical venous drainage with enlarged regional transmedullary veins developing as alternate pathways. It is postulated that inefficient outflow of venous blood causes chronic hypoxia that results in brain tissue loss and dystrophic calcifications. Abnormal innervation of the affected vasculature has also been reported and has been hypothesized to potentially exacerbate cerebral ischemia during times of increased metabolic demand (Cunha e Sa et al. 1997).

12.7.3 Diagnostic Criteria and Clinical Features

Two essential features of SWS are facial cutaneous nevi flammei (commonly known as "port-wine" stains) and leptomeningeal angiomas (Table 12.7) (Sudarsanam and Ardern-Holmes 2014; Menkes and Maria 2000). The other accepted name for port-wine stain is capillary vascular malformation. Skin findings are gener-

Table 12.7 Clinical features for Sturge–Weber syndrome (Bodensteiner and Roach 1999; Menkes and Maria 2000)

Major clinical features	Additional features
Congenital facial vascular nevus	Glaucoma/buphthalmos
Focal or generalized seizures	Neurologic deterioration
Brain MRI leptomeningeal enhancement after gadolinium administration plus enlarged transmedullary veins and unilateral hypertrophy of the choroid plexus	CT head parieto-occipital calcifications arranged in parallel lines "railroad tracks"

ally noticed at birth, and seizures may present in infancy. Classic manifestations include an ipsilateral facial port-wine stain, mental retardation, contralateral hemiparesis, contralateral hemiatrophy, and contralateral homonymous hemianopsia. Other features of the syndrome include glaucoma, dental abnormalities, and skeletal lesions. Migraine-like headaches, endocrinopathies such as central hypothyroidism and growth hormone deficiency, and frequent ear infections/sinus complaints have also been associated with SWS. Although the diagnosis of SWS is seldom difficult, challenges remain in predicting functional outcome (Waelchli et al. 2014; Oakes 1992; Maria et al. 1998a, b). The facial nevi are the most obvious of the possible manifestations of SWS, although the ipsilateral leptomeningeal angioma and related MRI abnormalities are regarded as the most important component in determining prognosis. Children with widespread vascular lesions often have more seizures and greater intellectual impairment. The SWS clinical triad consists of (1) seizure disorder, (2) mental retardation, and (3) facial angiomas.

Although facial nevi are relatively common malformations, occurring in approximately 3 in 1000 births, only 15 % of infants with typical port-wine cutaneous lesions have SWS. In fact, up to 85 % of patients with typical upper hemifacial nevi are not associated with leptomeningeal angiomatosis found classically in SWS. Conversely, 13 % of patients with cerebral manifestation of SWS do not display facial nevi. There is no correlation between size of facial involvement and CNS malformations (Bodensteiner and Roach 1999). Cutaneous facial nevi are usually present at birth but may become more prominent, thicker, and darker with age. Involvement of the eyelid is associated with ipsilateral brain involvement and usually conforms to the distribution of the first division of the trigeminal nerve. The second and third divisions of the trigeminal nerve can also be involved. A recent study has challenged the notion that risk of SWS in patients with facial nevi correlates with selective trigeminal nerve branch involvement, revealing instead a stronger correlation with patterns of embryonal vascular development in the region. Specifically, facial nevi involving skin of the upper eyelid and of the forehead (defined to be above a line connecting the outer ocular canthus and the top of the ear) were associated with the highest risk of underlying SWS (Waelchli et al. 2014). These observations are consistent with the current hypothesis that SWS occurs as a result of an acquired mutation during postzygotic vascular development.

Seizures often begin in the first year of life as the initial presenting feature in 80 % of patients with SWS and are often medically refractory (Maria et al. 1998a, b). Seizures usually arise focally at first but may secondarily generalize into tonic–clonic seizures. In addition, patients experience focal neurologic deficits that develop acutely in conjunction with flurries of seizures and also as Todd's paralysis that recovers more readily. Hemiparesis occurs with or without seizures and affected extremities often grow poorly, eventually resulting in hemiatrophy. Visual field defects result from involvement of one or both occipital lobes or optic tracts with leptomeningeal angiomatosis. Hydrocephalus may occur as a result of increased venous pressure from thromboses of deep venous channels or extensive arteriovenous anastomoses.

Mental retardation is common in SWS, with IQs lower than 90 in 70 % of patients (Menkes and Maria 2000). There is some controversy in the SWS literature regarding intellectual status. One study reports that all SWS patients without seizures are mentally normal (Sujansky and Conradi 1995). A conflicting study reports that although most infants with SWS have normal neurologic function, nearly all adults with SWS are impaired, suggesting a pervasive deterioration of function regardless of seizures (Maria et al. 1998a, b). The latter conclusion was supported by the study of a Spanish Sturge–Weber cohort, where 75 % of patients had IQ scores of 85 and lower. Functional impairment was evidenced by low levels of educational attainment in all patients, including those in whom seizures were controlled (Pascual-Castroviejo et al. 2008).

Other signs and symptoms of SWS include headaches, stroke-like episodes, contralateral hemiplegia, hemisensory deficits, and contralateral homonymous hemianopsia. Ocular involvement is common and includes glaucoma and buphthalmos (enlarged ocular globe) in up to 40 % of patients. The vascular malformations of the conjunctiva, episclera, choroid, and retina predispose to abnormal intra-globe fluid dynamics.

12.7.4 Natural History and Prognosis

SWS is associated with progressive CNS disease that results in seizures as well as motor, sensory, visual, and cognitive deficits. Early development of intractable seizures associated with hemiparesis and bilateral involvement are poor prognostic signs for cognitive development and general health. Recent studies showed that early white matter volume loss measured on brain MRI is associated with poor cognitive outcome (Juhasz et al. 2007).

12.7.5 Laboratory Studies

While recent efforts have identified a somatic *GNAQ* mutation (p.R183Q) as the presumed causative event in many cases of SWS, the diagnosis remains largely clinical. Urine biomarkers of neurologic function in SWS including MMP2, MMP9, and bFGF have been explored in preliminary studies and await further validation (Sreenivasan et al. 2013).

12.7.6 Imaging Studies

Although facial nevi are the most obvious manifestations of SWS, leptomeningeal angiomas are clearly the most important determinants of ultimate patient prognosis. Leptomeningeal malformations typically involve posterior cerebral hemispheres, especially occipital lobes. Such malformations cause ischemia in adjacent brain resulting in gliosis, demyelination, parallel cortical calcifications, focal cerebral atrophy, and hemiatrophy. Other findings include absent superficial cortical veins adjacent to the malformation and enlarged ipsilateral deep venous system choroid plexi.

Head CT scans reveal gyral or "tram-track" cortical calcifications (absent in very young patients), most commonly over posterior hemispheres. There is often underlying cortical atrophy. Enlargement of the skull, diploic space, subarachnoid space, sinuses, and mastoid air cells occurs ipsilateral to port-wine stains. Contrast-enhanced scans may reveal diffuse staining of involved cerebral cortex and intense leptomeningeal enhancement if performed prior to the development of cortical calcifications (Fischbein et al. 2000).

Brain MRI scans (Fischbein et al. 2000) demonstrate ipsilateral parenchymal atrophy, compensatory skull thickening, and sinus enlargement. There is marked gadolinium enhancement in areas of leptomeningeal angiomatosis. Enlargement of the ipsilateral choroid plexus occurs secondary to angiomatosis. T2 shortening in the white matter underlies angiomatous malformations, usually seen in infants, and may be due to ischemia. In later life, areas of T2 shortening are usually secondary to calcifications. Enlargement of deep venous structures occurs ipsilateral to meningeal angiomas. Advanced MRI techniques including susceptibility-weighted imaging and magnetic resonance spectroscopy, as well as functional imaging modalities with FDG-PET are increasingly being explored to improve lesion characterization and determine prognosis in SWS (Lo et al. 2013).

12.7.7 Treatment

Unlike other neurocutaneous syndromes, SWS is not associated with heightened predisposition to CNS tumors. Treatment of facial nevi has been revolutionized by vascular-specific pulsed dye laser therapy, and a recent small trial showed further increased efficacy with addition of topical

rapamycin (Marques et al. 2015). Ophthalmologic consultation is often required for aggressive medical and surgical management of glaucoma. If intractable seizures affect neurologic development and quality of life in young patients, there is general agreement that surgical resection (lobectomy, hemispherectomy) can significantly reduce seizure frequency and improve quality of life (Kossoff et al. 2002). This usually requires removal of the involved cortex and leptomeningeal abnormality. While prospective evidence is lacking, there is increasing retrospective data that low-dose aspirin therapy may be associated with decreased stroke-like episodes and seizures in SWS (Lance et al. 2013; Bay et al. 2011; Maria et al. 1998a, b).

Conclusions

The neurocutaneous syndromes are among the most common genetic disorders observed in humans. Furthermore, this unique group of patients is at higher risk for the development of CNS neoplasms. The responsible genes have already been identified for most disorders, although the molecular pathophysiology remains unclear in many cases. Please refer to Table 12.8 for up-to-date information. For the clinical oncologist, the challenge is the decision to treat or observe. Generally, this decision is driven by the tempo and severity of the patient's clinical picture, although a clear understanding of the natural history of the disease is essential. Fortunately, most patients do not develop malignant tumors, but this information is tempered by the need for lifelong observation and follow-up.

Table 12.8 Internet sites with additional information for the phakomatoses

Neurofibromatosis	www.ctf.org
Tuberous sclerosis	www.tsalliance.org
Ataxia telangiectasia	www.atsociety.org.uk www.atcp.org
Von Hippel–Lindau	www.vhl.org
Sturge–Weber	www.sturge-weber.com

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