Neuro-ophthalmic Features of the Neurocutaneous Syndromes

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Introduction

The neurocutaneous syndromes are a broad group of congenital and hereditary disorders with diverse genetic, clinical, and pathologic features that have developmental lesions of the skin and of the central and peripheral nervous systems in common. Many of these disorders are hamartomatous in nature, and produce benign tumors, but patients also may develop malignancies. The congenital disorders that have mutations in tumor suppressor genes, which predispose patients to have a higher frequency of malignancies include neurofibromatosis 1 (NF1), NF2, tuberous sclerosis, von Hippel-Lindau (VHL) disease, and ataxia telangiectasia (AT). Sturge-Weber disease is the only neurocutaneous syndrome that is not inherited.[1] This review will highlight the neuro-ophthalmic features of each disorder.

NF Type 1

NF1, an autosomal dominant disorder, is the most common phakomatosis, occurring in 1 of 5000.[2] The *NF1* gene is located on chromosome 17, encoding 2818 amino acid protein with a GTPase activator protein domain that functions as a tumor suppressor gene.[3] Its gene product, neurofibromin, causes aggregation of melanoblast precursors or Schwann cells during neural crest migration that lead to various hamartomatous and neoplastic lesions, such as malignant schwannomas.[4] The activation of the mammalian target of the rapamycin pathway is mediated by the phosphorylation and inactivation of the tuberous sclerosis complex 2 (TSC2)-encoded protein tuberin. This activated rapamycin pathway is involved in the development of NF1-related pilocytic astrocytomas.[3]

Some neuro-ophthalmic findings in NF1 are key distinguishing features from other phakomatoses. Lisch nodules, which are hamartomas of the iris pigment epithelium, are the most common ophthalmic

INTERNATIONAL OPHTHALMOLOGY CLINICS
Volume 52, Number 3, 73–85

feature of NF1, but are not pathognomonic of NF1. They are clear, yellow-brown, oval to round, dome-shaped papules that project from the surface of the iris. Lisch nodules become more prevalent with increasing age, about 50% at age 5 years, 75% at age 15 years, and 95% to 100% in adults over 30 years.[5]

Diplopia can be related to schwannomas and neurofibromas that most commonly affect cranial nerves III, followed by IV and VI. Cranial V involvement is also common, causing facial numbness.[6] Schwannomas encase nerves with myelin to cause localized compression and are usually benign. In contrast, a neurofibroma, composed of Schwann cells, perineural cells, and fibroblasts, infiltrates the nerve from which it arises.[6]

Proptosis can arise from schwannomas and neurofibromas in the orbit. Pulsatile proptosis with enophthalmos can occur when the sphenoid wing is absent; nonpulsatile proptosis is often associated with ipsilateral optic glioma or from a plexiform orbital neurofibroma. Strabismus and amblyopia can be complications of nonaxial proptosis. Neurofibromas of the upper eyelid are also associated with congenital glaucoma and can cause an S-shaped ptosis.[7]

Optic pathway gliomas (OPG), seen in about 15% to 20% of patients with NF1,[8] are usually low-grade pilocytic astrocytomas that may grow in the optic nerve (Fig. 1), optic chiasm, optic tract, and hypothalamus. Although these tumors may be histologically benign, asymptomatic, and nonprogressive, they account for significant morbidity in young children with NF1 because of visual loss, proptosis, and endocrine abnormalities associated with precocious puberty.[9] More than 2/3 of these tumors present by 7 years of age and most of these patients are asymptomatic.[10] When they become symptomatic, OPGs affecting the optic nerve may cause painless visual loss, proptosis, strabismus, and nystagmus. Visual loss varies from 20/20 to no light perception. Visual field defects include cecocentral scotomas (optic nerve), bitemporal hemianopsia (optic chiasm), and homonymous hemianopsia (retrochiasmal visual pathway). In addition to a relative afferent pupillary defect, optic disc edema (35%), optic atrophy (59%), choroidal folds, dyschromatopsia, ophthalmoplegia, and nystagmus (23%) are commonly seen in NF1.[10] When the tumor extends posteriorly to the hypothalamus, patients may have precocious puberty, hydrocephalus, headache, nausea, vomiting, and diplopia.[10] Magnetic resonance imaging (MRI) or computed tomographic (CT) scan of OPGs reveal fusiform enlargement of the optic nerve, kinking of the optic nerve, or enlargement and enhancement of the optic nerve, chiasm, or retrochiasmal visual pathways.[11,12]

All asymptomatic patients with NF1 younger than 8 years should undergo screening for OPG with an ophthalmologic examination. Although children of 8 years or older are at a lower risk of development of OPG, it is recommended that they undergo an ophthalmologic examination every 2 years until 18 years of age. Resection of OPGs may

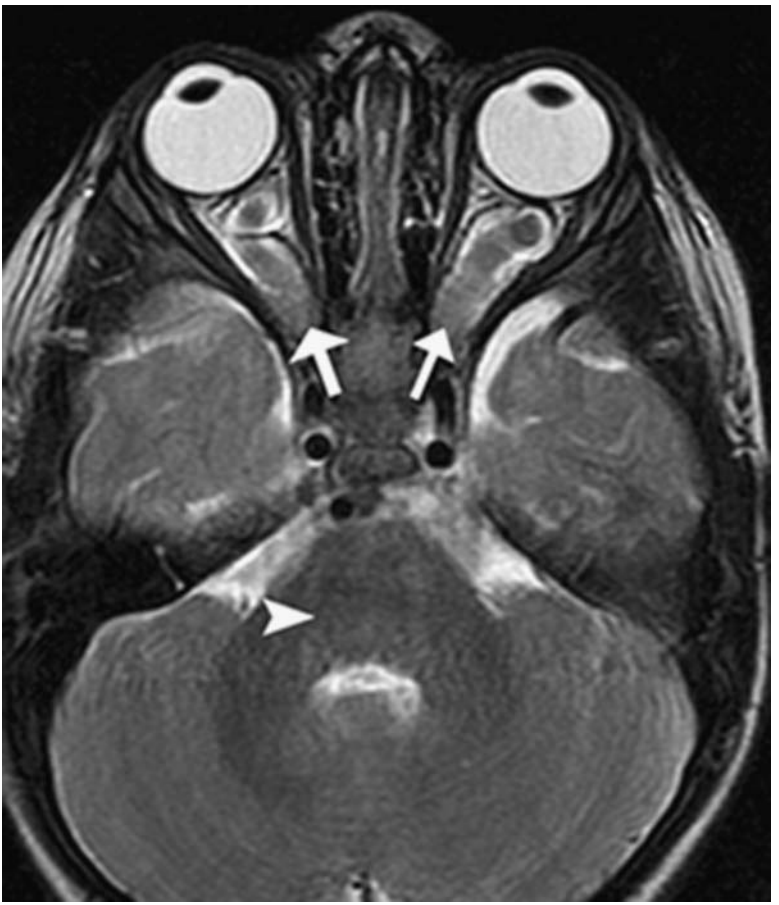

Figure 1. *Bilateral optic pathway gliomas in NF1. Axial T2-weighted magnetic resonance image shows diffuse enlargement and tortuosity of both optic nerves (arrows). Also note the ill-defined foci of T2 prolongation in the pons (arrowhead), which are consistent with neurofibromatosis spots representing myelin vacuolization. Courtesy of Ellen M. Chung, MD.*

be a treatment option in patients with poor or no vision and with severe proptosis because of cosmetic concerns or severe pain in a blind eye. Intrinsic chiasmal or retrochiasmal OPGs are considered not resectable, except for exophytic or cystic components. There has been no consensus on the definition of "progressive disease" (eg, radiographic evidence of tumor growth, decreasing visual function, or a combination of the 2), and some tumors even undergo spontaneous regression. Chemotherapy with vincristine and carboplatin is the recommended treatment for progressive NF1-associated OPG. Radiotherapy should be avoided because of the risk of secondary malignancies and radiation-induced vasculopathy. Secondary complications of hydrocephalus can be treated with a neurosurgical shunt.[9]

Table 1. *National Institutes of Health Clinical Diagnostic Criteria for NF1*[12]

Two or more of the following clinical features must be present:
≥6 café au lait macules of ≥5 mm in greatest diameter in prepubertal individuals, and >15 mm in greatest diameter in postpubertal individuals
≥2 neurofibromas of any type or 1 plexiform neurofibroma
Freckling in the axillary or inguinal regions
Optic glioma
≥2 iris hamartomas (Lisch nodules)
Bony lesion, such as sphenoid dysplasia or thinning of the long bone cortex with or without pseudoarthrosis
First-degree relative with NF1 based on the above criteria

NF indicates neurofibromatosis.

Systemic clinical features essential to the diagnosis of NF1 are summarized in Table 1.[2]

■ NF Type 2

NF2 is an autosomal dominant disorder and is less common than NF1 with a prevalence of about 1 in 50,000.[2] This disorder is characterized by the hallmark feature of bilateral vestibular schwannomas. Other features required for the diagnosis include a first-degree relative with NF2 with either unilateral eighth cranial nerve tumor or any 2 of the following: neurofibroma, glioma, meningioma, schwannoma, or juvenile onset posterior subcapsular cataracts.[2] The *NF2* gene on chromosome 22q11.2 encodes for a protein merlin that helps link actin cytoskeleton to cell surface glycoproteins controlling growth and cellular remodeling. This tumor suppressor gene is inactivated in NF2 mutations and leads to the development of schwannomas and meningiomas.[13]

Multiple epiretinal glial membranes are common in most patients with NF2. Some have choroidal hyperfluorescence of the posterior pole.[14] Other NF2 patients may have hamartomas affecting the retina and optic disc. In contrast, NF1 patients often have them involving the optic nerve and uveal tract.[2] Optic disc gliomas are also highly associated with NF2.[15] Juvenile posterior subcapsular cataracts, which are actually posterior cortical opacities extending posteriorly to the lens capsule, are seen in NF2 and not NF1.[16]

A suspected diagnosis of optic nerve sheath meningiomas (ONSM) suggests the need for further investigation for NF2. ONSM are highly associated with NF2 and are more invasive than the adult form in that they can extend into the orbit (Fig. 2). The most common presenting symptoms of ONSM are gradual progressive visual loss, visual field defects, proptosis, and upgaze restriction. Canalicular tumors present more often with generalized visual field constriction and very little proptosis. The optic disc is usually atrophic or swollen. Retinochoroidal (optociliary) shunt vessels are present in 15% to 33% of patients.

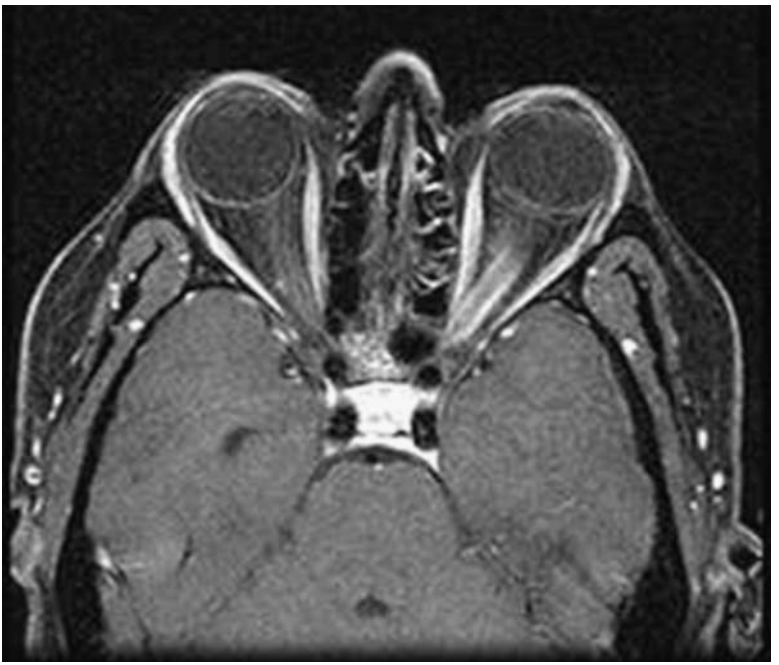

Figure 2. *Axial T1-weighted magnetic resonance imaging reveals a left optic nerve sheath meningioma.*

Neuroimaging reveals diffuse, tubular enlargement of the optic nerve. Unlike optic gliomas, kinking of the optic nerve (a classic neuroimaging sign of optic glioma) is not seen in ONSMs. On CT scan calcification along the length of the optic nerve may be seen in 20% to 30% of patients and is sometimes referred to as a "tram-track sign." On MRI the tumor is isointense with brain on T1 and T2-weighted images and enhances homogeneously with gadolinium.[17]

For NF2-associated ONSM, orbital surgery is recommended when tumor progression is seen on MRI or when the affected eye develops proptosis or pain. If the ONSM presents as an isolated finding in the orbit associated with good vision, then observation for any visual or radiographic progression is recommended. If progression is noted, 3-dimensional conformal radiotherapy may be a better option than surgery in some treatment centers.[17]

Bilateral vestibular schwannomas occur in about 95% of patients with NF2. They often become apparent after visual symptoms develop and often remain asymptomatic until young adulthood. These tumors may cause unilateral or bilateral progressive hearing loss followed by tinnitus and imbalance. Diplopia may later develop from compression of the sixth cranial nerve, facial sensory loss from the fifth nerve, and facial palsy from the seventh nerve.[18]

Table 2. *National Institutes of Health Clinical Diagnostic Criteria for NF2*[2]

One of the following clinical features must be present:
Bilateral vestibular schwannomas
First-degree relative with NF2 and unilateral vestibular schwannoma or any 2 of the following: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities
Unilateral vestibular schwannoma and any 2 of the following: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities
Multiple meningiomas and unilateral vestibular schwannoma or any 2 of the following: schwannoma, glioma, neurofibroma, cataract

NF indicates neurofibromatosis.

It is recommended that medical evaluation be performed at 10 to 12 years of age to include MRI of brain and spine, slit lamp examination, audiogram, family history, and examination of first-degree relatives.[18] The systemic clinical features essential to the diagnosis of NF2 are summarized in Table 2.[2]

■ Tuberous Sclerosis

TSC is an autosomal dominant disorder, but up to 60% of cases have no family history and are thought to represent spontaneous mutations and associated with advanced paternal age.[19] The estimated prevalence is 1 in 10,000 to 1 in 26,500.[20] Tuberous sclerosis is genetically heterogeneous, in which 60% to 80% of mutations are related to 2 genes: the *TSC1* gene on chromosome 9 encodes for the protein hamartin[21] and the *TSC2* gene on chromosome 16 encodes for the protein tuberin.[22] TSC1 mutations occur more often in familial cases. TSC2 mutations are more often associated with sporadic cases and more severe disease.[23]

Astrocytic hamartomas of the retina and optic nerve are seen in tuberous sclerosis in about 40% to 50% of individuals. They may be bilateral in 34% to 50% of cases. They rarely lead to visual loss, unless they are located in the macula or a vitreous hemorrhage develops. These lesions initially appear as a smooth, translucent, gray, focally elevated lesion and some may later calcify to mimic optic disc drusen, especially when located on the surface of the disc. The noncalcified hamartomas are the most common and are usually found in the posterior retinal pole. Calcified, nodular, mulberry lesions are typically found at or near the disc margin[24] (Fig. 3). Unlike drusen, optical coherence tomography reveals that retinal hamartomas are hyperreflective with disorganized retinal layers, "moth-eaten" spaces, and posterior shadowing.[25] Those hamartomas located in the retina can mimic toxoplasmosis, toxocariasis, and retinoblastoma. Fluorescein angiography reveals superficial vascularization of the tumor during the venous phase and late staining.[26] Pigmentary retinal abnormalities, such as punched-out areas of retinal

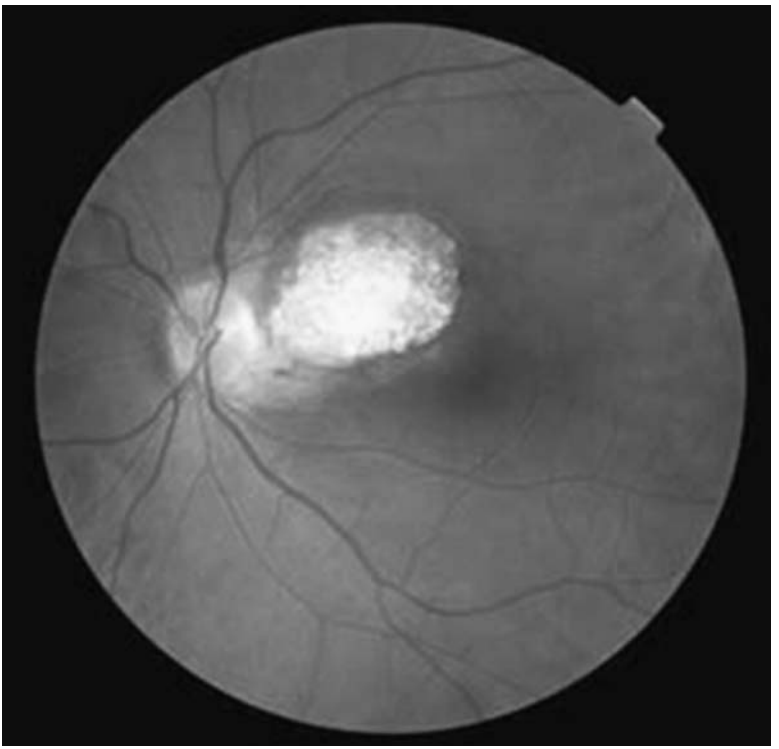

Figure 3. *Astrocytic hamartoma adjacent to left optic disc. Courtesy of William F. Hoyt, MD.*

depigmentation, plaque-like lesions in the deep retina, and pigment clumping may also be seen.[24]

Other nonretinal manifestations include early-onset cataracts, hamartomas of the iris pigment epithelium and ciliary body epithelium, eyelid angiofibromas, strabismus, colobomas, and iris depigmentation.[26]

Cortical tubers appear as hyperintense T2 nodules on brain MRI. Subependymal nodules, which are asymptomatic, are often located along the lateral aspect of the ventricles between the thalamus and caudate nucleus. They can become calcified with age and may be better visualized on CT than MRI. Up to 15% may develop into subependymal giant cell astrocytomas.[27]

Initial evaluation for children suspected of TSC includes screening for seizures, neurodevelopmental testing, ophthalmologic examination, skin examination in normal light and with a Wood's lamp, MRI of brain, electrocardiogram, and renal ultrasound. Gene mutational analysis for TSC1 and TSC2, detectable in 60% to 80% of affected patients, is commercially available for diagnosis of atypical cases and for genetic counseling. Systemic features essential for the diagnosis of TSC are summarized in Table 3.[28] Treatment of complications of TSC is primarily

Table 3. *Revised Diagnostic Criteria for Tuberous Sclerosis Complex*[28]

Major features
Facial angiofibromas or forehead plaque
Nontraumatic ungula or periungual fibroma
≥ 3 hypomelanotic macules
Shagreen patch (connective tissue nevus)
Multiple retinal nodular hamartomas
Cortical tuber
Subependymal nodule
Subependymal giant cell astrocytoma
Single or multiple cardiac rhabdomyomas
Lymphangiomyomatosis
Renal angiomyolipoma
Minor features
Multiple, randomly distributed pits in dental enamel
Hamartomatous rectal polyps
Bone cysts
Cerebral white matter radial migration lines
Gingival fibromas
Nonrenal hamartoma
Retinal achromic patch
"Confetti" skin lesions
Multiple renal cysts
Definite tuberous sclerosis complex: either 2 major features or 1 major feature plus 2 minor features
Probable tuberous sclerosis complex: 1 major and 1 minor feature
Possible tuberous sclerosis complex: either 1 major feature or ≥2 minor features

symptomatic at this time. Everolimus, an inhibitor of mammalian target of rapamycin, was recently approved by the Food and Drug Administration for TSC patients with subependymal giant cell astrocytomas who were not candidates for surgical resection (http://www.fda.gov).

■ Sturge-Weber Syndrome

Unlike the other neurocutaneous syndromes, Sturge-Weber syndrome is not an inherited disorder. The facial hemangioma, or *nevus flammeus*, is composed of venous dilatations with no capillary proliferation. The blood vessels are derived from the choroid, meninges, and face. The deoxygenated blood in these venous channels gives the port-wine color to these lesions.[29]

Glaucoma affects the eye ipsilateral to the facial telangiectasia in 30% of cases and may lead to optic atrophy, buphthalmos, anisometropia, and amblyopia usually within the first 2 years of life. Increased intraocular pressure is thought to be related to elevated episcleral venous pressure or to trabeculodysgenesis. Glaucomatous optic neuropathy and buphthalmos are more commonly associated with hemangioma of the upper lid.[30]

The leptomeningeal vascular malformation is similar to and ipsilateral to the facial lesion. It is located between the pia and arachnoid membranes in the occipitoparietal region, and can extend anteriorly. Underlying cortical veins are absent or nonfunctioning, causing abnormal cerebral venous drainage. The underlying cerebral cortex gradually becomes atrophic and calcium deposits form in the vessels and superficial cortex. These processes may lead to homonymous hemianopsia, positive visual symptoms related to seizures, and hemiparesis. Impaired cerebrospinal fluid absorption can also lead to elevated intracranial pressure, papilledema, and headaches.[31]

The diagnosis of Sturge-Weber syndrome is based on demonstration of the facial and leptomeningeal angiomata. MRI of the brain with contrast may reveal enhancement of the meningeal angioma and enlarged choroid plexus in the lateral ventricle ispilateral to the facial hemangioma. No specific treatment exists for this disorder, except for laser therapy for the port wine stain and medications for glaucoma and seizures. Prognosis depends upon the extent of the leptomeningeal angioma and its effect on cerebral cortex perfusion, and the severity of ocular involvement.[31]

■ VHL Disease

VHL disease is an autosomal dominant disorder characterized by retinal angiomas, cerebellar hemangioblastomas, renal cell carcinoma, pheochromocytoma, and epididymal cystadenoma.[32] The tumor suppressor gene, *VHL1*, is located on chromosome 3p26,[33] encoding for a protein that regulates hypoxia-inducible genes. Overexpression of hypoxia-inducible mRNAs, such as vascular endothelial growth factor, leads to the high vascularization of VHL-related tumors.[34]

The hallmark feature of VHL disease is the retinal capillary hemangioma, a red vascular tumor consisting of a small feeder arteriole and draining venule that gradually enlarge and become globular. "Twin vessels," in which 2 blood vessels are separated by less than 1 venule width and run parallel or overlapping each other, are a reliable retinal sign for VHL syndrome. These lesions often develop in the temporal peripheral retina and are bilateral in about half of cases.[35] Retinal capillary hemangiomas are often detected in the second or third decade of life, before central nervous system hemangiomas or other systemic tumors. Although they can be treated with retinal cryotherapy or laser photoablation, depending upon their size and location, they have a tendency to recur.[36]

Hemangioblastomas may occur in other regions of the visual pathway and in the central nervous system. They may be located in the optic nerve or chiasm causing optic neuropathy or proptosis. Sixty

Table 4. *Diagnostic Criteria for von Hippel-Lindau Disease*[39]

A single hemangioblastoma of the central nervous system or retina and a visceral manifestation (multiple renal, pancreatic, or hepatic cysts; pheochromocytoma, renal carcinoma)
Definite family history and any one of the above manifestations
Presence of von Hippel-Lindau gene mutation

percent of patients develop a cerebellar hemangioblastoma during the third decade of life. Its growth can lead to increased intracranial pressure with neuro-ophthalmic signs, such as papilledema, sixth nerve palsy, dorsal midbrain syndrome, and downbeat nystagmus.[37] Treatment of these vascular tumors with angiogenesis inhibitors is currently being investigated.[38]

Systemic features essential for the diagnosis of VHL disease are summarized in Table 4.[39] VHL disease has 2 genetic variants. Type 1 involves the development of pheochromocytoma and type 2 does not. Types 1 and 2B (with renal carcinoma) are the most common subtypes that have a greater tendency to have retinal capillary hemangioblastomas.[39] Type 2A (without renal carcinoma) is least likely to have retinal lesions and has the best visual prognosis.[35]

Recent case reports show that antiangiogenic agents, such as intravitreal bevacizumab, pegaptanib, and ranibizumab, along with photodynamic therapy resulted in a decrease in exudation, tumor regression, and improved visual acuity. Whether vascular endothelial growth factor is the ideal target in the inhibition of VHL-related tumor, growth is still unproven.[40]

■ Ataxia Telangiectasia

AT is an autosomal recessive disorder that is characterized by cerebellar ataxia, skin and eye telangiectasias, immune deficiency, and a tendency to develop malignancies. The genes for AT map to chromosome 11q22-11q23,[41] encoding proteins involved in mitogenic signal transduction, meiotic recombination, and cell cycle control.[42]

Bilateral bulbar conjunctival telangiectasias are the classic neuro-ophthalmic features of AT that develop between 3 to 5 years of age. These telangiectasias are located within the palpebral fissure and have aneurysmal dilatations with sharp turns.[43]

Eye movement disorders related to cerebellar degeneration develop later. Impaired gaze holding, impaired smooth pursuit, and cancellation of vestibular slow phases are probably related to dysfunction of the cerebellar flocculus and paraflocculus. Ocular motor apraxia is the defective saccadic initiation and fixation disturbance in which saccades have prolonged latency and hypometric amplitude, and compensatory head movements are used to initiate gaze shifts.[44]

Table 5. *Diagnostic Criteria for Ataxia Telangiectasia*[44]

Definitive diagnosis
Increased radiation-induced chromosomal breakage in cultured cells or progressive cerebellar ataxia with mutations on both alleles of ATM
Probable-progressive cerebellar ataxia with 3 of the following 4 features:
1. Ocular or facial telangiectasia
2. Serum IgA at least 2 SD below normal for age
3. Alpha fetoprotein at least 2 SD above normal for age
4. Increased radiation-induced chromosomal breakage in cultured cells
Possible progressive cerebellar ataxia with at least 1 of the following 4 features:
1. Ocular or facial telangiectasia
2. Serum IgA at least 2 SD below normal for age
3. Alpha fetoprotein at least 2 SD above normal for age
4. Increased chromosomal breakage after exposure to radiation

Progressive cerebellar ataxia develops in early childhood at around 5 to 6 years of age. Movement disorders, such as choreoathetosis, myoclonic jerks, and dystonia, also appear later. The increased sensitivity of chromosome breakage with ionizing radiation and gene rearrangement leads to the higher risk of developing malignancies. Almost all patients have persistently elevated α-fetoprotein levels. Frequent sinopulmonary infections predispose to pulmonary failure as the most common cause of death.[44] MRI of the brain reveals vermian atrophy with an enlarged fourth ventricle and cisterna magna with minimal cerebellar hemispheric atrophy.[45] The diagnostic criteria for AT are summarized in Table 5.[44]

■ Summary

This review highlights the diagnostic criteria and neuro-ophthalmic symptoms and signs of the more commonly seen neurocutaneous disorders, including NF1 and NF2, tuberous sclerosis, VHL disease, Sturge-Weber disease, and AT. The distinct neuro-ophthalmic features in each of these hereditary and congenital disorders play an important role in clinical diagnosis.

The author declares that there are no conflicts of interest to disclose.

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