Neurocristopathies: Enigmatic Appearances of Neural Crest Cell–derived Abnormalities

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Abbreviations: CHARGE = *c*olobomas of the iris, *h*eart defects, *a*tresia of the choanae, *r*etarded growth, *g*enital hypoplasia, and *e*ar anomalies; HFM-GS = hemifacial microsomia–Goldenhar syndrome, MEN = multiple endocrine neoplasia, MTC = medullary thyroid carcinoma, NCC = neural crest cell, NCM = neurocutaneous melanocytosis, NCP = neurocristopathy, NF1 = neurofibromatosis type 1, TCS = Treacher Collins syndrome

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SA-CME LEARNING OBJECTIVES

After completing this journal-based SA-CME activity, participants will be able to:

- Describe the basic developmental features of the neural crest and NCCs.
- Discuss the embryologic basis of prototypic NCPs.
- List the imaging features of several NCPs.

See rsna.org/learning-center-rg.

The neural crest is an important transient structure that develops during embryogenesis in vertebrates. Neural crest cells are multipotent progenitor cells that migrate and develop into a diverse range of cells and tissues throughout the body. Although neural crest cells originate from the ectoderm, they can differentiate into mesodermal-type or endodermal-type cells and tissues. Some of these tissues include the peripheral, autonomic, and enteric nervous systems; chromaffin cells of the adrenal medulla; smooth muscles of the intracranial blood vessels; melanocytes of the skin; cartilage and bones of the face; and parafollicular cells of the thyroid gland. Neurocristopathies are a group of diseases caused by the abnormal generation, migration, or differentiation of neural crest cells. They often involve multiple organ systems in a single person, are often familial, and can be associated with the development of neoplasms. As understanding of the neural crest has advanced, many seemingly disparate diseases, such Treacher Collins syndrome, 22q11.2 deletion syndrome, Hirschsprung disease, neuroblastoma, neurocutaneous melanocytosis, and neurofibromatosis, have come to be recognized as neurocristopathies. Neurocristopathies can be divided into three main categories: dysgenetic malformations, neoplasms, and combined dysgenetic and neoplastic syndromes. In this article, neural crest development, as well as several associated dysgenetic, neoplastic, and combined neurocristopathies, are reviewed. Neurocristopathies often have clinical manifestations in multiple organ systems, and radiologists are positioned to have significant roles in the initial diagnosis of these disorders, evaluation of subclinical associated lesions, creation of treatment plans, and patient follow-up.

Online supplemental material is available for this article.

Introduction

In 1974, Robert Bolande described a group of seemingly disparate diseases with a shared developmental origin: the neural crest. These diseases included neuroblastoma, pheochromocytoma, medullary thyroid carcinoma (MTC), Hirschsprung disease, neurofibromatosis type 1 (NF1), and multiple endocrine neoplasia (MEN) syndrome. Bolande used the umbrella term *neurocristopathy* (NCP) to refer to any among this group of diseases (1).

Neural crest cells (NCCs) contribute to form a variety of cells and tissues, including cells of the peripheral, autonomic, and enteric nervous systems; cartilage and bone of the face; and tissues of the eye, heart, thyroid gland, and adrenal glands (Table 1) (2). During embryogenesis, abnormalities in the generation, migration, and differentiation of NCCs can lead to a variety of diseases that we currently recognize as NCPs (1,3,4). Because understanding of neural crest development has advanced in recent years, the number of diseases recognized as NCPs has increased significantly. Many craniofacial

TEACHING POINTS

- The neural crest appears late during embryonic development and is seen only in vertebrates. NCCs are transient multipotent progenitor cells that arise from the neural crest, between the neural plate and nonneural ectoderm, during gastrulation and neurulation. After induction, NCCs undergo an epithelial to mesenchymal transition, delaminate from the neural crest, and migrate to various parts of the embryo to develop into a diverse range of cells and tissues throughout the body.
- Many seemingly unrelated diseases, including craniofacial, endocrine, immunologic, cardiac, gastrointestinal, dermatologic, and neoplastic conditions, are now recognized as NCC-related abnormalities and have been consolidated under the term *neurocristopathy*.
- Facial dysostoses are a set of clinically and etiologically heterogeneous congenital craniofacial anomalies. Many of these disorders occur as a consequence of the abnormal development of the first and second pharyngeal arches and their derivatives during embryogenesis. TCS and Goldenhar syndrome are prototypic facial dysostoses.
- 22q11.2 Deletion syndrome is a dysgenetic NCP of cranial and vagal neural crest origin. It is caused by abnormal development of the third and fourth pharyngeal arches and the third pharyngeal pouch and results in multiorgan disorders, including cardiovascular, immunologic, and endocrine abnormalities.
- Neural crest derivatives give rise to neuroblastomas, pheochromocytomas and extra-adrenal paragangliomas, melanomas, and MTCs. These tumors can be sporadic or occur as components of hereditary syndromes.

anomalies, as well as endocrine, immunologic, cardiac, gastrointestinal, dermatologic, and neoplastic conditions, are now recognized as NCPs (Table E1) (4,5).

NCPs often involve multiple organ systems in a single individual, tend to occur in families with significant phenotypic variability, and can be associated with the development of neoplasms. Radiologists are in a unique position to have significant roles in the initial diagnosis of NCP, evaluation of subclinical associated lesions, creation of treatment plans, and follow-up of patients with NCPs.

Owing to the variety of NCPs that are now recognized, it is beyond the scope of this article to provide a comprehensive review of all of these diseases. Instead, we review some of the more well-understood NCPs, with examples of dysgenetic, neoplastic, and combined (dysgenetic and neoplastic) forms of these diseases.

Neural Crest Cells

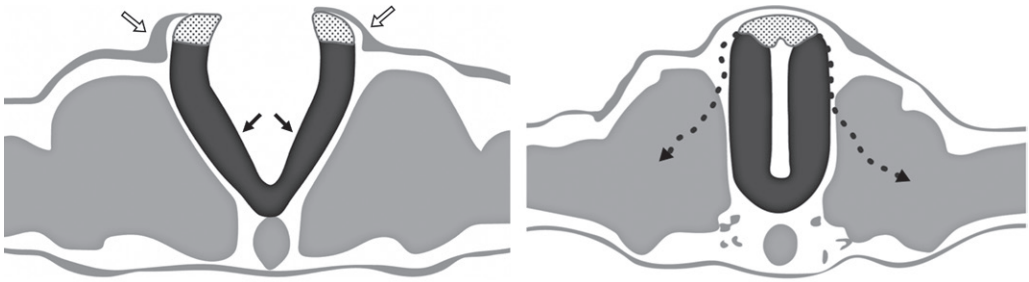
The neural crest appears late during embryonic development and is seen only in vertebrates (6). NCCs are transient multipotent progenitor cells that arise from the neural crest, between the neural plate and nonneural ectoderm, during gastrulation and neurulation (Fig 1). After induction, NCCs undergo an epithelial to mesenchymal transition, delaminate from the neural crest, and migrate to various parts of the embryo to develop into a diverse range of cells and tissues throughout the body (2,3,7,8).

The neural crest can be divided into four segments—the cranial, vagal, trunk, and sacral segments—according to the location of the segment

Table 1: Cells and Tissues Derived from NCCs

Derived from cranial NCCs
Cartilage and bone of skull and face*
Nerve ganglia
Adenohypophyses
Vascular smooth muscle cells*
Carotid artery bodies
Connective tissues*
Eye tissues (corneal endothelium and stroma, trabecular meshwork, iris stroma, ciliary body stroma, anterior sclera)*
Lacrimal glands
Dental pulp*
Pigment cells*
Hair follicles
Olfactory epithelium
Adipocytes*
Cranial meninges*
Derived from vagal NCCs
Cardiac tissue*
Aortopulmonary septum*
Innervation of lung
Enteric ganglia of gut
Peripheral nervous system
Melanocytes*
Thyroid stroma*
Thyroid C cells
Thymus†
Parathyroid gland†
Cardiac ganglia
Derived from trunk NCCs
Neurons and glia of dorsal root and sympathetic ganglia
Schwann cells of ventral roots
Schwann cells of islet of Langerhans
Chromaffin cells of adrenal medulla
Melanocytes*
Neurons of enteric nervous system
Derived from sacral NCCs
Enteric ganglia
Sympathetic ganglia
Lower urogenital tract innervation

*Mesodermal-type cells.
†Endodermal-type cells.



a. b.

Figure 1. Drawings of the neural crest anatomy. **(a)** The neural crest (dotted areas) develops at the junction of the neural plate (black arrows) and nonneural ectoderm (white arrows). **(b)** After closure of the neural plate, NCCs (dotted arrows) delaminate from the neural crest and migrate extensively to prescribed destinations throughout the embryo.

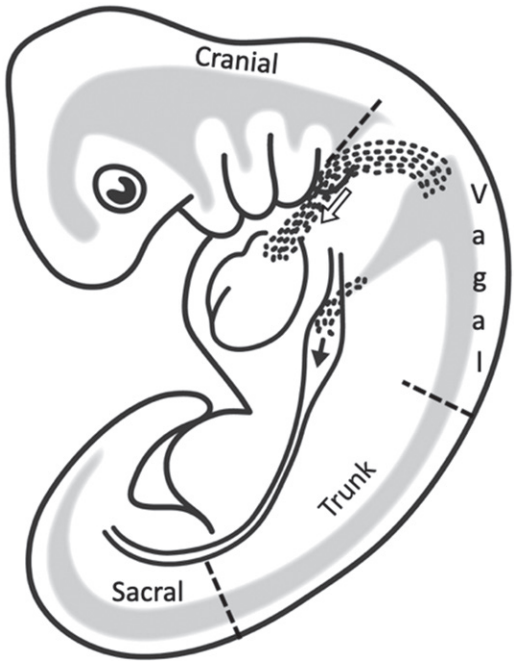


Figure 2. Drawing depicts segments of the neural crest in the developing embryo. Vagal NCCs migrate to cardiac tissue (white arrow), the enteric neural plexus (black arrow), and other locations.

along the cephalocaudal axis of the embryo (Fig 2). NCCs follow a prescribed pattern of migration that is based on the final cell type (2,7). For example, melanocyte precursor cells follow a lateral pathway superficial to the dermomyotome and migrate to the skin, whereas neurogenic precursors, which eventually form the dorsal root ganglia, sympathetic ganglia, and enteric neural plexus, follow a medial pathway underneath the dermomyotome to reach their final destinations (Fig 3) (5,9).

In the traditional germ layer model, endodermal cells differentiate into endodermal derivatives, and mesodermal cells differentiate into mesodermal derivatives, etc. Although NCCs originate from the ectoderm, many NCC derivatives differentiate into mesodermal or endodermal tissues (Table 1) (10). This capacity of NCCs for multidirectional differentiation contradicts the traditional "germ layer law," which infers the mutual exclusivity of the fates of the three primary germ layers (2).

Because of the late appearance of NCCs during embryonic development, the capacity of these cells for multidirectional differentiation, and the diffuse pervasiveness of NCC derivatives throughout the body, the neural crest can be considered "the fourth germ layer" in addition to the primary germ layers of the ectoderm, mesoderm, and endoderm (11).

Neurocristopathies

NCPs are a group of diseases that are caused by NCC abnormalities that manifest during embryonic development. As the understanding of neural crest development has advanced in recent years, the number and variety of NCPs have rapidly grown to include more than 50 diseases (Table E1) (4,12). Many seemingly unrelated diseases, including craniofacial, endocrine, immunologic, cardiac, gastrointestinal, dermatologic, and neoplastic conditions, are now recognized as NCC-related abnormalities and have been consolidated under the term *neurocristopathy.*

NCPs can be divided into three main categories: dysgenetic malformations caused by abnormal NCC development, NCC neoplasms, and combined dysgenetic and neoplastic syndromes (Table 2) (1,13). Both dysgenetic and neoplastic NCPs can occur in a sporadic or syndromic fashion.

While defects in the primary germ layers often result in fetal demise, many infants with NCC defects are born alive with congenital anomalies. The effect of primary germ layer defects and neural crest defects can be explained by using the analogy of building a house. If there are defects in the structural elements (primary germ layers) of the house, then it cannot stand (fetal demise). On the other hand, if the structural elements

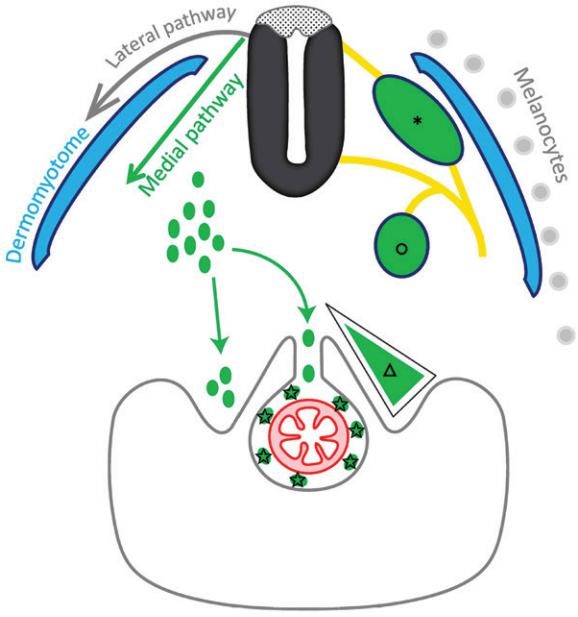


Figure 3. Drawing depicts the migration pathways of various NCCs. Melanocyte precursors take a lateral pathway superficial to the dermomyotome and extend to the skin. Neurogenic precursors (green dots) take the medial pathway under the dermomyotome and form the dorsal root ganglions (*), sympathetic ganglions (○), adrenal medulla (△), and enteric neural plexus (☆).

are intact, the house can stand, but it may have defective furniture (NCPs).

Dysgenetic NCPs

NCPs Involving Primarily Cranial NCCs

Cranial NCCs migrate predominantly to the first and second pharyngeal arches. The first pharyngeal arch gives rise to the maxilla, zygoma, palate, mandible, malleus, incus, fifth cranial nerve, and muscles of mastication. The second pharyngeal arch gives rise to the hyoid cartilage, stapes, seventh cranial nerve, and facial expression muscles. The first pharyngeal cleft forms the external auditory meatus, whereas the first pharyngeal pouch develops into the middle ear cavity and eustachian tube (Table 3). Malformations of the first and second pharyngeal arches typically manifest at birth as maxillary, zygomatic, and mandibular hypoplasia; cleft palate; and/or auricular defects (14,15). Cranial NCPs include Treacher Collins syndrome (TCS) and hemifacial microsomia–Goldenhar syndrome (HFM-GS) spectrum.

Facial dysostoses are a set of clinically and etiologically heterogeneous congenital craniofacial anomalies. Many of these disorders occur as a consequence of the abnormal development of the first and second pharyngeal arches and their derivatives during embryogenesis (16). TCS and Goldenhar syndrome are prototypic facial dysostoses.

Table 2: NCP Classifications and Examples

Dysgenetic NCPs
Pigmentation anomalies
Abnormal angiogenesis
Facial dysostoses
22q11.2 deletion syndrome
CHARGE syndrome
Hirschsprung disease
Neoplastic NCPs
Neuroblastoma
Pheochromocytomas and paragangliomas
MTC
Melanocytosis and melanoma
Neurofibroma and schwannoma
Mixed dysgenetic and neoplastic NCPs
Familial neuroblastoma, pheochromocytoma and paraganglioma, MTC
Combined congenital central hypoventilation syndrome, Hirschsprung disease, and neuroblastoma
MEN 2 syndromes
NCM
Neurocutaneous syndromes

Note.—CHARGE = *c*olobomas of the iris, *h*eart defects, *a*tresia of the choanae, *r*etarded growth, *g*enital hypoplasia, and *e*ar anomalies; NCM = neurocutaneous melanocytosis.

Treacher Collins Syndrome.—TCS is a prototypic facial dysostosis and NCP of cranial neural crest origin. This syndrome was first described in 1900 by Edward Treacher Collins, an English ophthalmologist. It affects one in 50 000 live births. More than 90% of TCS cases are caused by autosomal dominant mutations of the *TCOF1* gene located on chromosome 5. Up to 60% of cases result from sporadic mutations. *TCOF1* encodes the treacle protein, which is essential for proliferation and formation of cranial NCCs. Mutations of *TCOF1* result in abnormal development of the first and second pharyngeal arches (17).

In TCS, craniofacial defects are usually bilateral and symmetric. The characteristic facial features of TCS include micrognathia and midface hypoplasia that are most substantial in the maxilla, mandible, and zygoma (Figs 4, 5) (18). Inferolateral orbital clefts cause downward slanting of the palpebral fissures and colobomas of the lateral lower eyelids (15). The majority of affected individuals have a high arched palate, which frequently has a cleft (18).

The cranial NCCs contribute substantially to the development of the external and middle ears. Greater than 80% of individuals with TCS demonstrate abnormal development of the auricle,

Table 3: Derivatives of Pharyngeal Region

Derivative Type	Derivative Structure(s)
First pharyngeal cleft	External auditory canal
Pharyngeal arches	
First arch	Maxillary artery
	Cranial nerve V
	Masticator muscles
	Bone structures: malleus, incus, zygoma, maxilla, mandible
Second arch	Hyoid and stapedial arteries
	Cranial nerve VII
	Facial expression muscles
	Bone structures: stapes, styloid process, stylohyoid ligament, hyoid cartilage
Third arch	Internal carotid artery
	Cranial nerve IX
	Stylopharyngeus muscle
	Hyoid cartilage
Fourth arch	Conotruncal vessels
	Cranial nerve X
	Pharyngeal and laryngeal muscles
	Laryngeal cartilage
Pharyngeal pouches	
First pouch	Middle ear
	Eustachian tube
Second pouch	Supratonsillar fossa
Third pouch	Thymus
	Parathyroid gland

external auditory canal, ossicles, and middle ear cavity (Figs 6, 7). The inner ear structures, which are derived from the mesoderm and ectoderm, are generally preserved in individuals with TCS (19).

Facial dysostoses have serious functional, aesthetic, and social consequences that require lifelong medical and surgical management. A comprehensive multidisciplinary team that includes plastic surgery, oral surgery, dentistry, otolaryngology, audiology, speech and language pathology, genetics, pediatrics, social work, and nursing staff is required to treat and reduce a lifetime of complex problems. Radiologists are in a position to take an active role in the initial diagnosis, treatment planning, and follow-up of patients with TCS (20).

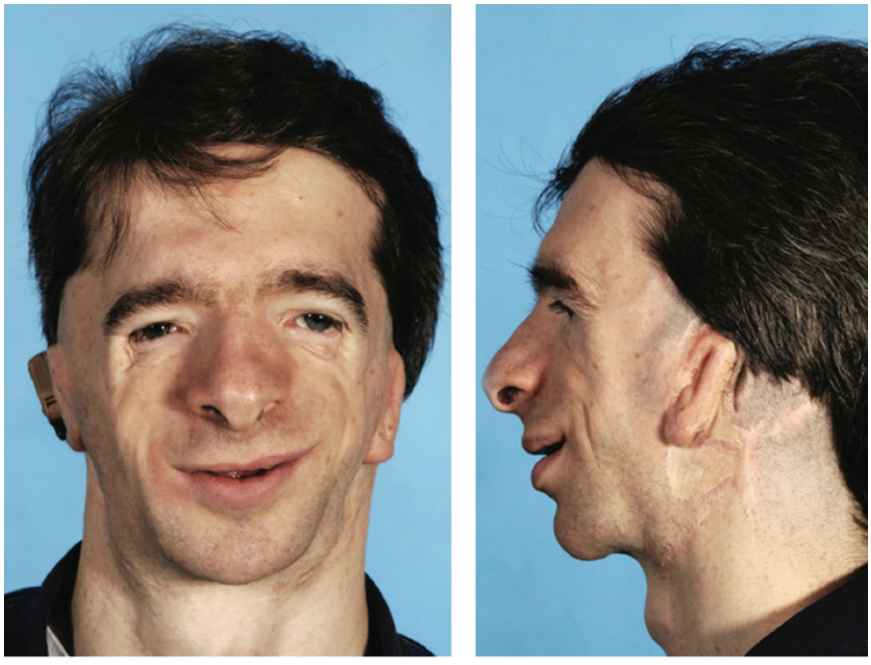
HFM-GS Spectrum.—Goldenhar syndrome is characterized by unilateral hypoplasia of various derivatives of the first and second pharyngeal arches, and it predominantly involves the right side (Fig 8). The phenotypes are highly variable and range from milder unilateral facial hypoplasia (ie, hemifacial microsomia) to more complex cases involving cardiac, vertebral, and central nervous system anomalies (21). Goldenhar syndrome consists of hemifacial microsomia, with more extensive involvement associated with epibulbar dermoid cysts and vertebral anomalies (22). Hemifacial microsomia is the second most common facial dysostosis after cleft lip and palate.

The incidence of HFM-GS spectrum ranges from one in 3600 to one in 5600 live births for milder cases, to one in 20 000 for more severe cases (23). Results of gene mapping in patients with HFM-GS spectrum have indicated a link to a region on chromosome 14q32 (24). Embryonic vascular compromise of the stapedial artery (a derivative of the second pharyngeal arch) has been implicated and explains the unilateral nature of the involvement (21).

In HFM-GS spectrum, involvement of structures beyond the first and second pharyngeal arch derivatives are seen. This involvement includes abnormal development of the internal carotid artery, inner ear, and brain (Fig 9) (25). The internal carotid artery may be hypoplastic or absent (Fig 10). Various degrees of cochlear and/or vestibular anomalies and abnormal cranial nerve development also have been reported (26).

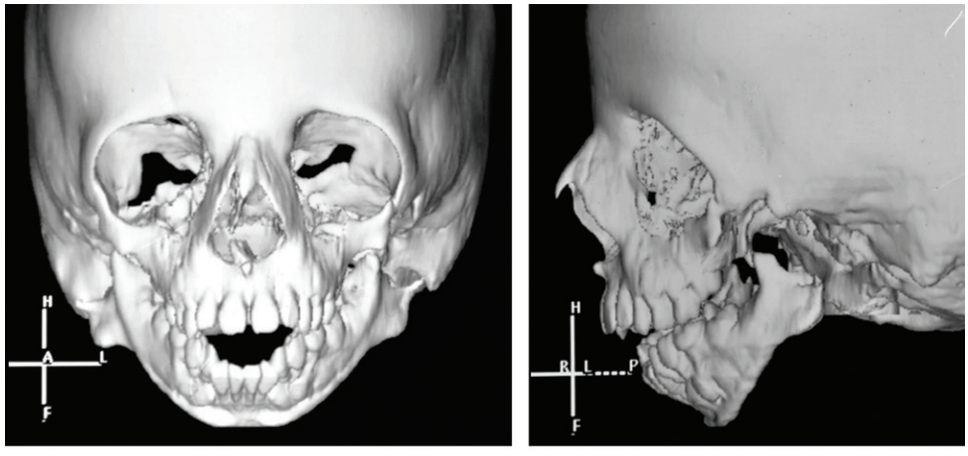
NCPs Primarily Involving Vagal NCCs

A large population of vagal NCCs migrate to the third and fourth pharyngeal arches (16). The third pharyngeal arch forms cranial nerve IX, the stylopharyngeus muscle, and parts of the hyoid cartilage, while the fourth pharyngeal arch forms cranial nerve X, the pharyngeal and laryngeal



a. b.

Figure 4. Photographs show the characteristic facial appearance of TCS in a man. Frontal **(a)** and lateral **(b)** clinical photographs show micrognathia, midface hypoplasia, and downward slanting of the eyes. In addition, the lower eyelashes are missing, and a partially reconstructed auricular defect is seen. (Reprinted, with permission, from reference 17.)



a. b.

Figure 5. Frontal **(a)** and lateral **(b)** reconstructed CT images of the face of a 6-year-old boy with TCS show hypoplasia of the maxilla, zygoma, and mandible, with an anterior open bite.

musculature, and the laryngeal cartilage (Table 3). Another important contribution of the fourth pharyngeal arch is formation of the conotruncal vessels, right ventricle, and cardiac conduction system (27). The third pharyngeal pouch forms the thymus and parathyroid gland. Vagal NCPs include 22q11.2 deletion syndrome, CHARGE syndrome, and Hirschsprung disease.

22q11.2 Deletion Syndrome.—22q11.2 Deletion syndrome is a dysgenetic NCP of cranial and vagal neural crest origin. It is caused by abnormal development of the third and fourth pharyngeal arches and the third pharyngeal pouch and results in multiorgan disorders, including cardiovascular, immunologic, and endocrine abnormalities. 22q11.2

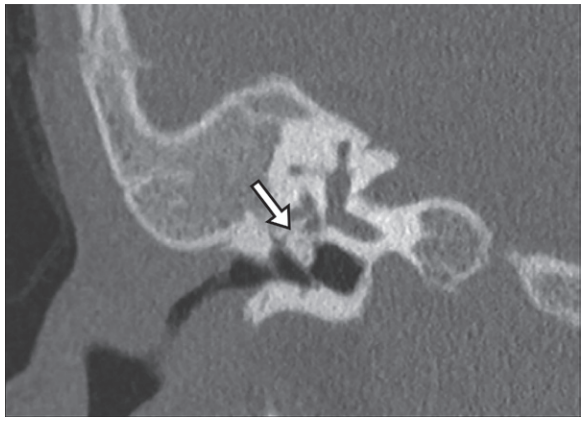


Figure 6. Temporal bone findings in a 5-year-old girl with TCS. Coronal CT image of the right temporal bone shows stenosis of the external auditory canal, with dysplastic ossicles (arrow) adhered to the lateral wall of a contracted middle ear chamber.

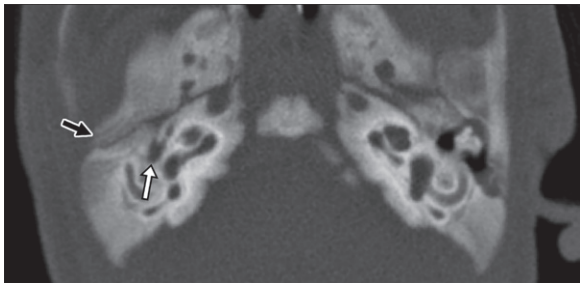
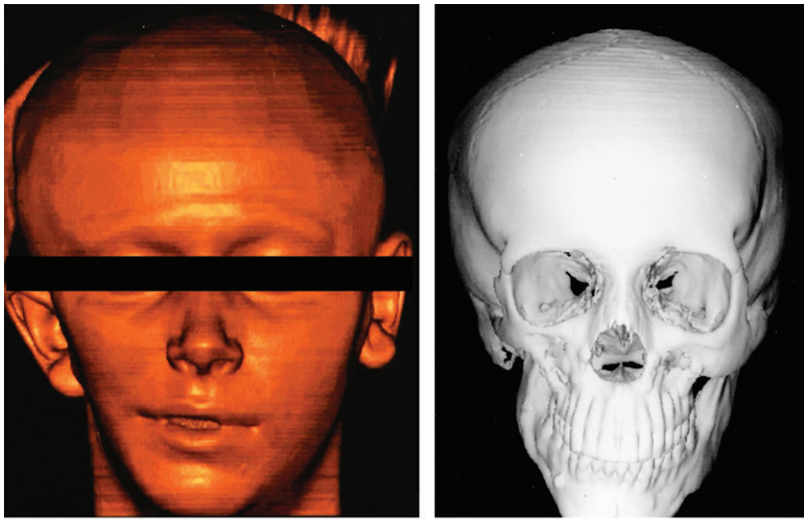


Figure 7. Axial CT image in a 1-year-old child with TCS shows bony atresia of the right external auditory canal (black arrow), with a contracted middle ear chamber and ossicular aplasia (white arrow).



a. **b.**

Figure 8. Facial appearance of a child with Goldenhar syndrome. Frontal soft-tissue **(a)** and bone **(b)** three-dimensional CT reconstruction images show right hemifacial microsomia, with hypoplasia of the zygoma, maxilla, and mandible.

deletion syndrome is common and occurs in one in 4000 live births (28). This syndrome was first described in 1965 by Angelo DiGeorge, a Philadelphia endocrinologist who reported the congenital absence of the thymus and parathyroid glands in a group of infants. Subsequently, facial dysmorphism, conotruncal cardiac malformations, and speech delay also were identified in these patients and referred to under various names, including velocardiofacial syndrome, cardiofacial syndrome, and conotruncal anomaly face syndrome (28).

It is now known that 90% of individuals have a microdeletion at chromosome 22q11.2. Deletion of the *TBX1* gene is thought to be responsible for many of the characteristic findings of 22q11.2 deletion syndrome (29). Currently, the term *DiGeorge syndrome* is reserved for the rare disease specrum in persons who share this clinical phenotype but do not have a 22q11.2 deletion (30).

TBX1 is important in the development of the embryonic pharyngeal system, with mutations causing severe hypoplasia or aplasia of the second to fourth pharyngeal arches, sixth pharyngeal arch, second to fourth pharyngeal pouches, and pharynx. The thymus and parathyroid gland are derived from the third pharyngeal pouch, whereas the conotruncal vessels are derived from the fourth pharyngeal arch (30,31).

The clinical features of 22q11.2 delection syndrome vary widely among patients and affect multiple organ systems. Symptoms often include congenital heart defects (usually conotruncal abnormalities such as interrupted aortic arch [Fig 11], truncus arteriosus, and tetralogy of Fallot), palatal defects, feeding difficulty secondary to velopharyngeal insufficiency (due to both structural and functional abnormalities of the pharyngeal and laryngeal structures), learning disabilities, immunodeficiency with recurrent infections (due to an absent or hypoplastic thymus and impaired T-cell production), seizures (due to hypocalcemia from malfunctioning parathyroid glands), and renal anomalies (28,30). Early-onset Parkinson disease and increased rates of schizophrenia also have been reported (32). Because of the varied clinical manifestations of 22q11.2 deletion syndrome, it is important to have a high index of suspicion when these conditions are encountered in clinical practice (30). Radiologists may be the first to recognize the common thread in this multisystemic disease and make the correct diagnosis.

CHARGE Syndrome.—CHARGE syndrome is another NCP involving derivatives of the cranial and vagal NCCs. It affects approximately one in 10 000 births. CHARGE syndrome was first

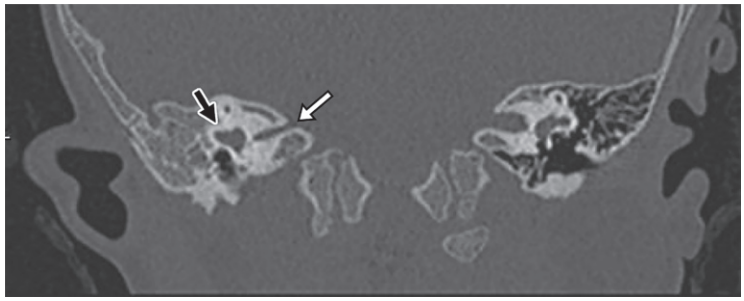


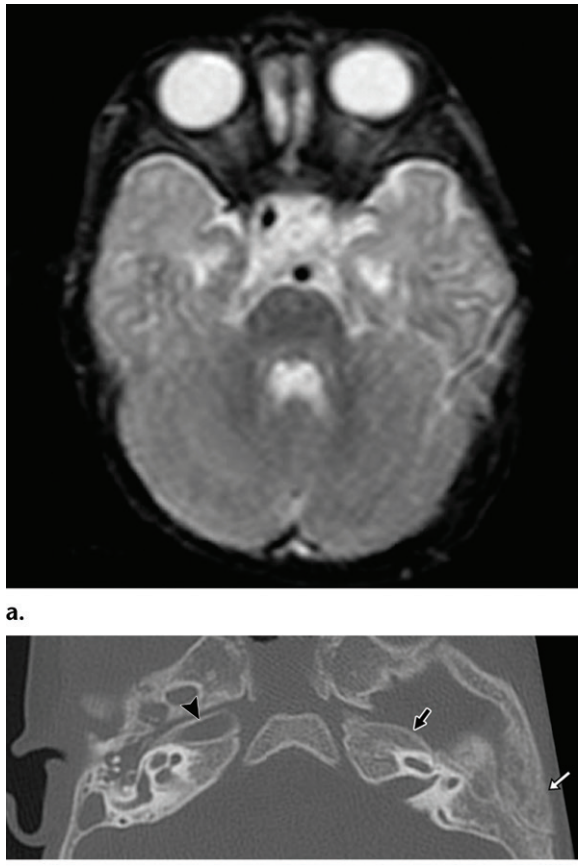
Figure 9. Temporal bone findings in a 1-year-old girl with Goldenhar syndrome. Coronal CT image shows right internal auditory canal stenosis (white arrow), with dysplasia of the right lateral semicircular canal and vestibule (black arrow). (Courtesy of Dr Mikiko Miyakasa, National Center for Child Health and Development Hospital, Tokyo, Japan.)

characterized in 1979 as a constellation of nonrandomly associated malformations (*c*olobomas of the iris [Fig 12], *h*eart defects, *a*tresia of the choanae, *r*etarded growth, *g*enital hypoplasia, and *e*ar anomalies). Many clinical features of CHARGE syndrome, including conotruncal cardiac defects, immune deficiency, cognitive and motor delays, cleft lip and palate, and renal abnormalities, overlap with the clinical features of 22q11.2 deletion syndrome (33).

Approximately two out of three individuals with CHARGE syndrome have been found to have mutations of the *CHD7* gene (34). These mutations are usually sporadic (35). Mutations of the *CHD7* gene in CHARGE syndrome appear to affect a broader range of craniofacial development than does 22q11.2 deletion syndrome, with development of not only NCCs but also neuroectodermal elements. In 80% of individuals with CHARGE syndrome, the disease is associated with middle ear dysplasia, suggesting abnormal development of the first and second pharyngeal arches (36,37).

The *CHD7* gene has an important role in inner ear development as well. Hypoplasia and aplasia of the semicircular canals is seen in almost all cases of CHARGE syndrome (Figs 13, 14) (36–38). Other inner ear anomalies include vestibular and/or cochlear dysplasia and cranial nerve VIII hypoplasia. *CHD7* has also been implicated in the normal development of the olfactory bulb and multiple other cranial nerves, including cranial nerves VII–X (38).

Hirschsprung Disease.—Hirschsprung disease is a common NCP of vagal and sacral neural crest origin. It affects one in 5000 births, with a male-to-female ratio of 4:1 (39). Hirschsprung disease is characterized by the absence of enteric ganglion cells in the myenteric (Auerbach) and submucosal (Meissner) plexus. This disorder involves the rectum or rectosigmoid region but can extend farther and may involve the entire colon (Fig 15). Hirschsprung disease commonly occurs in neonates with bowel obstruction, but it can manifest in older individuals who have chronic constipation or enterocolitis (40).



a.

b.

Figure 10. Goldenhar syndrome and left internal carotid artery agenesis in a 2-year-old girl. **(a)** Axial T2-weighted MR image shows an absence of left internal carotid artery flow. **(b)** Axial temporal bone CT image shows a normal right carotid canal (arrowhead) and absent left carotid canal (black arrow), confirming agenesis of the internal carotid artery. Left-sided external auditory canal atresia (white arrow) also is seen. (Case courtesy of Dr Mikiko Miyakasa, National Center for Child Health and Development Hospital, Tokyo, Japan.)

Neurogenic precursors for the enteric neural plexus originate mainly from vagal NCCs and take a medial pathway underneath the dermomyotome to reach the mesenteric root. They then migrate along the intestinal tract from the rostral to caudal aspect and eventually reach the rectum (9). Migrational arrest at 8 weeks gestation results in total colonic aganglionosis, whereas arrest at 10–12 weeks gestation results in rectosigmoid aganglionosis (41,42).

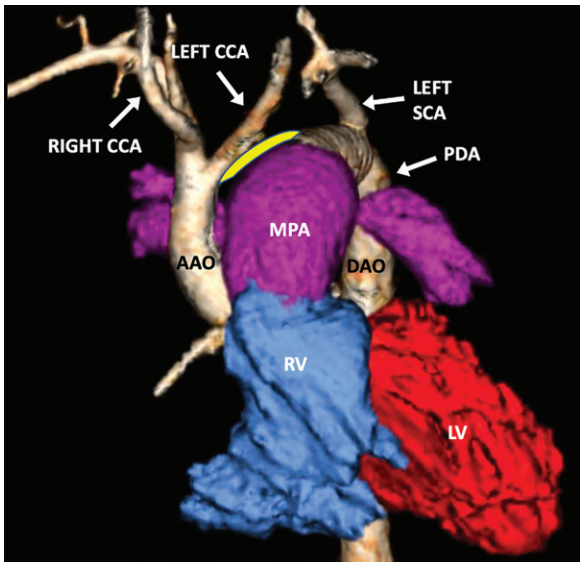


Figure 11. Anteroposterior three-dimensional volume-rendered CT image in a newborn with a type B interrupted aortic arch shows discontinuity of the ascending aorta *(AAO)* and descending aorta *(DAO)*, with the ascending aorta demonstrating continuity with the brachiocephalic artery and left common carotid artery *(CCA)*. A patent ductus arteriosus *(PDA)* supplies blood to the left subclavian artery *(SCA)* and descending aorta. Yellow region represents an area of discontinuity in the aorta. *LV* = left ventricle, *MPA* = main pulmonary artery, *RV* = right ventricle.

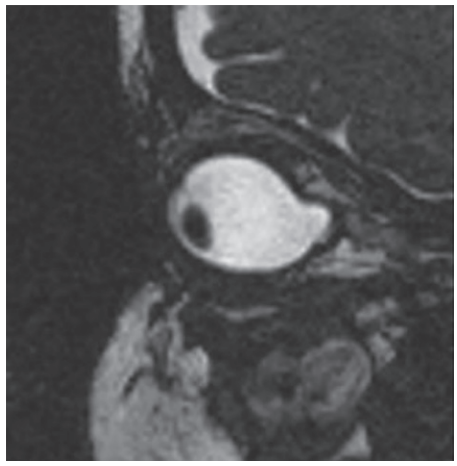


Figure 12. Sagittal T2-weighted MR image in a neonate with CHARGE syndrome shows an ocular coloboma.

The genetic features of Hirschsprung disease are multifactorial, and multiple genes, including *RET, EDNRB, SOX10,* and *PHOX2B*, have been implicated. The majority of cases of Hirschsprung disease are sporadic, with 10% of cases being caused by germline mutations. An increased prevalence of *RET* mutation is found among individuals who have familial and long-segment Hirschsprung disease. This anomaly is also known to be associated with other NCPs, such as Waardenburg syndrome (multicolored irises, forelock of white hair, wide-set eyes, broad nasal root, and sensorineural deafness) and congenital central hypoventilation syndrome (absent initiation of increased breathing under hypercapnic or hypoxic conditions). In Waardenburg syndrome type IV, mutations of the *SOX10* gene have been known to cause Hirschsprung disease owing to the inability of defective vagal NCCs to form the enteric neural plexus within the bowel (43). Hirschsprung disease is seen in up to 20% of persons with congenital central hypoventilation syndrome, in whom mutations in the *PHOX2B* gene have been implicated (44).

NCPs Involving Broad Segments of the Neural Crest

Melanocyte Abnormalities

Melanocyte precursor NCCs have a broad origin encompassing the cranial, vagal, truncal, and sacral neural crest segments and migrate along the lateral pathway outside the dermomyotome, reaching the dermo-epidermal junction of the skin and meninges of the brain (9). Hyperpigmentation disorders of the skin are some of the most common manifestations of NCP and may be components of more complex NCPs. Benign lesions include ephelides, pigmented moles, nevi, and lentiginosis. Although these lesions are initially dysgenetic, with increased epidermal colonization of melanocytes or melanocyte precursors, mutagenic events later in life may cause neoplastic transformation to melanoma (45).

Neurocutaneous Melanocytosis

NCM is a rare sporadic NCP that can involve all neural crest segments (46). NCM was first described in 1861 and is characterized by the presence of congenital melanocytic nevi on the skin and melanocytic tumors in the leptomeninges of the central nervous system (47).

Melanocytic deposition in the leptomeninges of the brain is initially asymptomatic, but two-thirds of affected individuals eventually develop communicating hydrocephalus with symptoms of increased intracranial pressure. Melanocytic depositions in the meninges develop into melanoma in more than half of individuals with NCM (47).

Although the exact pathogenesis of NCM is unknown, several factors are believed to contribute to its development. Hepatocyte growth factor–scatter factor is a cytokine that has an important role in the proliferation and distribution of melanocytes. Deregulation of hepatocyte growth factor–scatter factor is believed to lead to increased development of melanoblasts, which then migrate to the meninges as precursors to benign or malignant melanocytes (48). Mutations of the *NRAS* gene also have

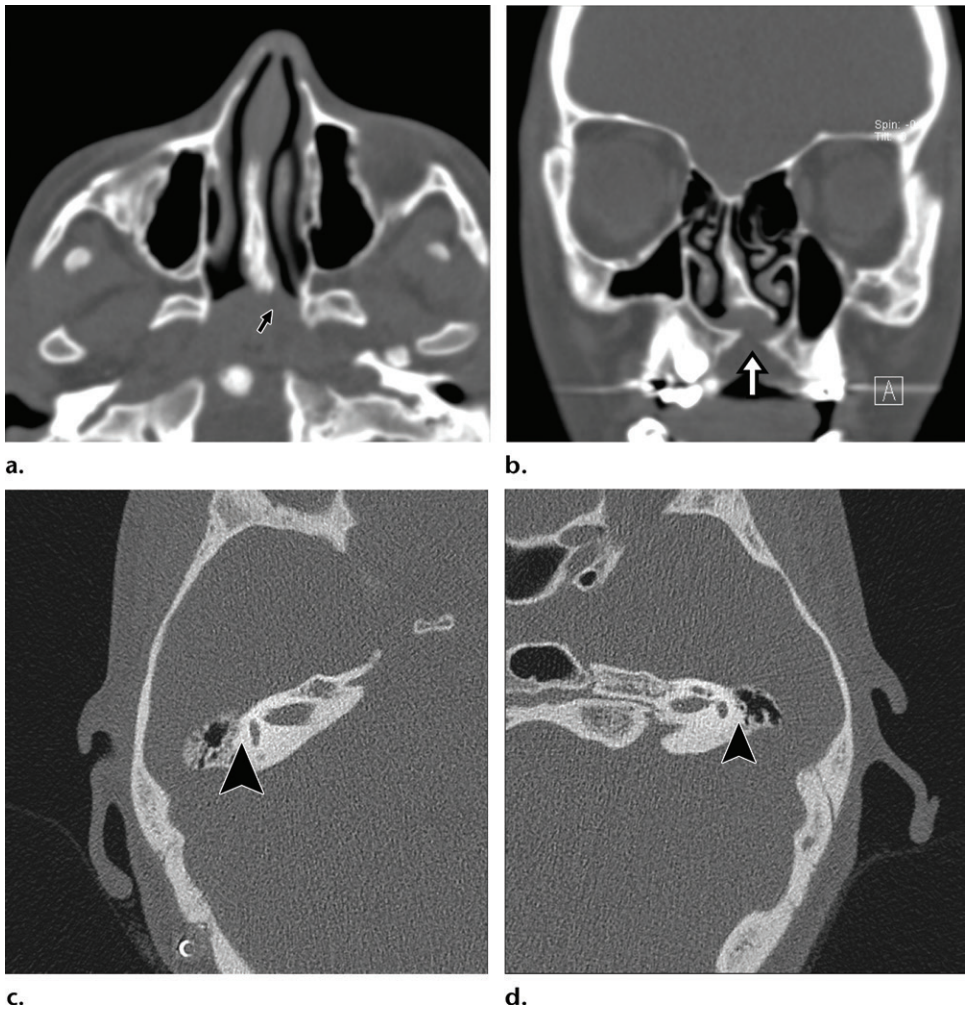


Figure 13. CHARGE syndrome with sensorineural hearing loss in an 18-year-old woman. **(a, b)** Axial **(a)** and coronal **(b)** CT images show left-sided choanal stenosis (arrow in **a**) and cleft palate (arrow in **b**). **(c, d)** Axial temporal bone CT images show bilateral absence of the lateral semicircular canals (arrowhead).

been found in individuals with congenital melanocytic nevi and those with melanocytic tumors of the central nervous system (49).

Common sites of intracranial melanin accumulation in persons with NCM include the meninges, anterior temporal lobes, amygdala, thalami, pons, and cerebellum. Also, Dandy Walker malformations in up to 10% of individuals with NCM have been reported (46). Meningeal enhancement usually is not apparent until the development of melanoma (50). Spinal involvement may be seen in up to 20% of cases and may include arachnoid cysts, lipomas, and tethered cords (47).

Up to 45% of persons with congenital giant melanocytic nevi are found to have NCM (51). Screening brain MRI is recommended for all individuals with congenital giant melanocytic nevi. Screening MRI should be performed before the infant is aged 4 months, as T1 hyperintensity of melanin deposition in the brain is more conspicuous before the progression of myelination (Fig 16) (52).

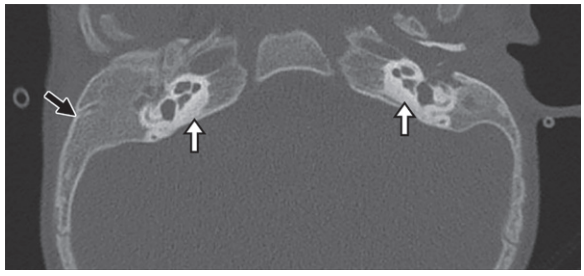
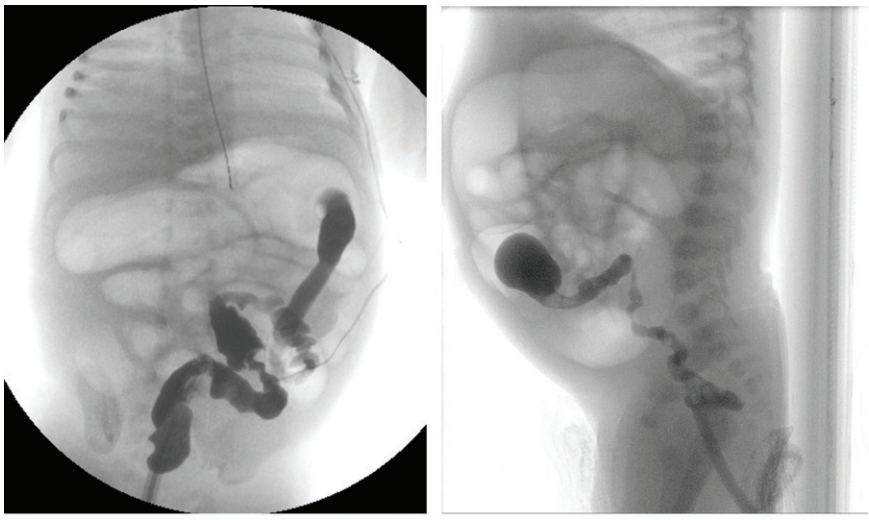


Figure 14. CHARGE syndrome with bilateral sensorineural hearing loss in a 1-year-old child. Axial temporal bone CT image shows bilateral agenesis of the internal auditory canals (white arrows) and bony atresia of the right external auditory canal (black arrow).

Neoplastic NCPs

Neurogenic precursors of the vagal and truncal neural crest contribute to development of the sympathetic ganglia, adrenal medulla, and enteric nervous system. Neural crest derivatives give rise to neuroblastomas, pheochromocytomas and extra-adrenal paragangliomas, melanomas, and



a. b.

Figure 15. Hirschsprung disease in a neonate who did not pass meconium. Anteroposterior **(a)** and lateral **(b)** images obtained at barium enema examination show a narrowed rectosigmoid colon and descending colon, which were evaluated at biopsy, which revealed long-segment Hirschsprung disease. The sister and brother of this baby were diagnosed with Hirschsprung disease at infancy, and two cousins also had this disease. This strong family history suggested a genetic component of the Hirschsprung disease in this newborn.

MTCs. These tumors can be sporadic or occur as components of hereditary syndromes (4).

Neuroblastoma

Neuroblastomas are the most common solid pediatric malignancies; they arise from the adrenal medulla and sympathetic nervous system (53). Neurogenic precursors originate from the vagal and truncal neural crest and form the autonomic ganglia and adrenal medulla. In neuroblastoma, neuroblast development is dysregulated by genetic, epigenetic, and/or chemical pressures such as aberrant expression of the *MYCN* oncogene leading to the generation of tumor-initiating neuroblasts (54).

The majority of neuroblastomas are sporadic, but 1%–2% of them are inherited in an autosomal dominant fashion. Persons with familial neuroblastoma often have multiple primary tumor sites and an earlier age of onset (Fig 17). The germline mutations found in these individuals include those of the *PHOX2B* and *ALK* genes (53). Neuroblastoma is also known to occur with other NCPs, including congenital central hypoventilation syndrome (CCHS), Hirschsprung disease, Waardenburg syndrome type IV, and 22q11.2 deletion syndrome (55,56). The association between neuroblastoma and Hirschsprung disease is particularly prominent in individuals with CCHS. In addition, the incidences of Hirschsprung disease and neuroblastoma are 500–1000 times greater in persons with CCHS than in the general population (57–59).

Pheochromocytoma and Paraganglioma

Pheochromocytoma and paraganglioma are neuroendocrine tumors of neural crest origin that are derived from the chromaffin cells of the sympathetic and parasympathetic division of the autonomic nervous system (60,61). Tumors originating from the adrenal medulla are referred to as pheochromocytomas, while those of an extra-adrenal origin are referred to as paragangliomas. Approximately 100–200 cases of childhood pheochromocytoma or paraganglioma are reported every year in the United States. The average age of children when these tumors manifest is 11–13 years (60). Pheochromocytomas or paragangliomas originating from the sympathetic ganglia usually are catecholamine secreting, while those originating from the parasympathetic ganglia rarely produce significant amounts of catecholamines (62). This feature has important implications in terms of clinical manifestions, imaging, and therapy.

Pheochromocytomas and paragangliomas originating from the sympathetic axis typically arise from the adrenal medulla (the largest sympathetic ganglia of the body), retroperitoneum, or posterior mediastinum. Pheochromocytomas and paragangliomas originating from the parasympathetic axis usually occur in the head and neck region and the middle and anterior mediastinum (63).

Classic symptoms of a catecholamine-secreting pheochromocytoma or paraganglioma include hypertension with diaphoresis, headaches, and episodic palpitations (60). A nonsecreting pheochromocytoma or paraganglioma in the head or neck may be found incidentally during imaging

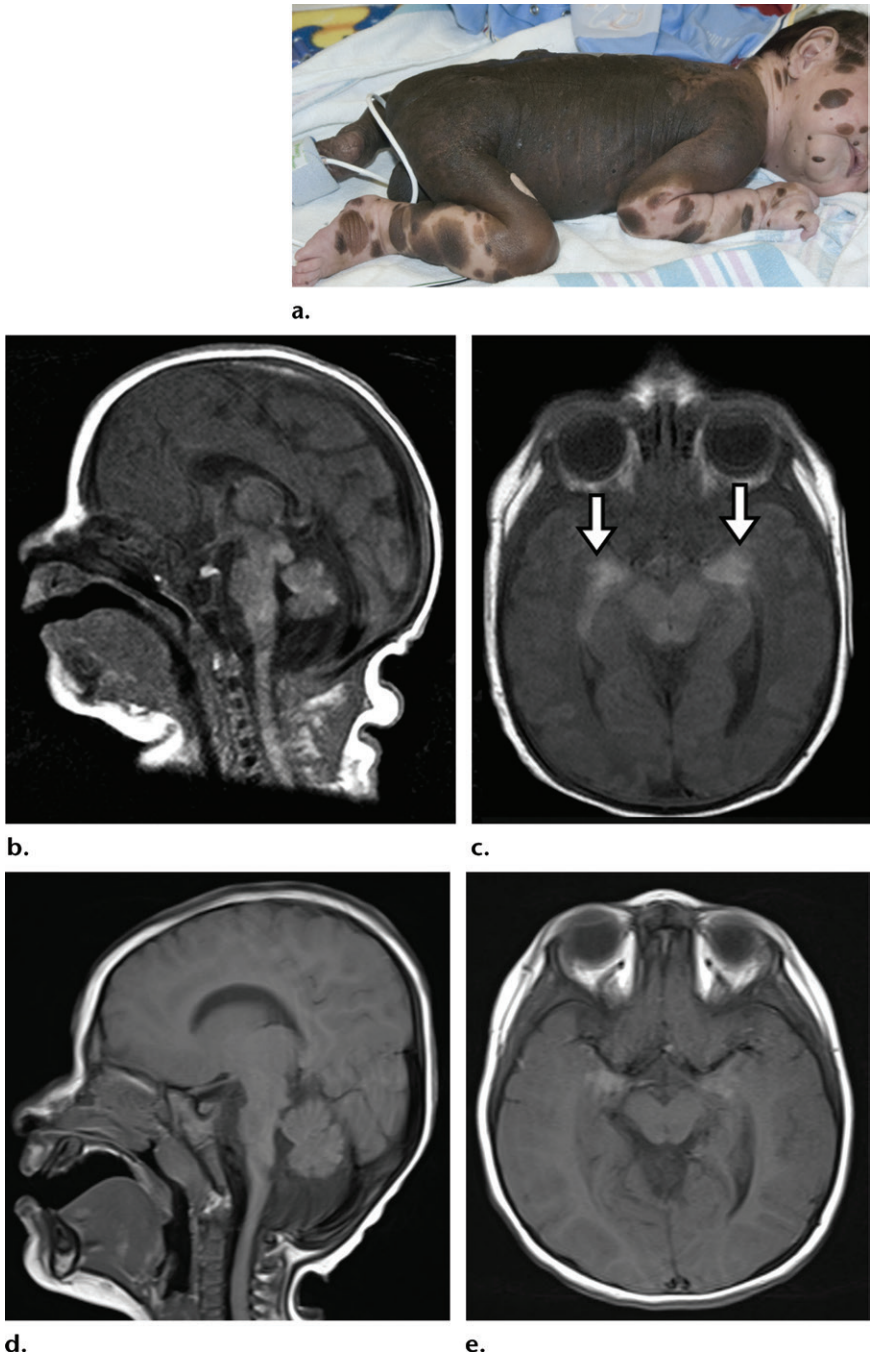


Figure 16. NCM in a child with a congenital giant melanocytic nevus at birth. **(a)** Clinical photograph of the newborn shows a congenital giant melanocytic nevus with multiple satellite lesions. **(b, c)** Sagittal **(b)** and axial **(c)** T1-weighted MR images in the newborn at 1 week of age show melanocytic deposits in the amygdala (arrows in **c**), diencephalon, brainstem, and cerebellum. The cerebellum is hypoplastic, with a posterior fossa cyst that is continuous with the fourth ventricle through the hypoplastic inferior vermis. **(d, e)** Follow-up sagittal **(d)** and axial **(e)** T1-weighted MR images in the child at age 3 years show decreased conspicuity of the signal intensity abnormalities as myelination of the background brain tissue progresses.

performed for other indications or manifest with symptoms such as hearing loss, tinnitus, dysphagia, and cranial nerve palsies secondary to mass effect from tumors (61).

Up to 40% of cases of pediatric pheochromocytoma or paraganglioma are familial, whereas only 10% of adult cases are familial. Familial pheochromocytomas and paragangliomas are more likely to be multifocal and recurrent. Genetic counseling and testing are recommended for all individuals with these tumors (62). Examinations of patients with familial pheochromocytomas or paragangliomas have revealed germline mutations of the *SDHx*, *VHL*, *RET*, and *NF1* genes. Carney-Stratakis (ie, Carney dyad) syndrome, which manifests with pheochromocytomas or paragangliomas, and gastrointestinal stromal tumors, is another disorder associated with these tumors (60).

According to Endocrine Society guidelines, biochemical tests, including analyses to determine free plasma or urinary metanephrine levels, should be performed for diagnosis confirmation before anatomic imaging. CT or MRI can be performed for anatomic localization, although functional nuclear medicine imaging can yield functional and treatment information (64). Indications for functional nuclear medicine imaging include confirmation of the diagnosis of pheo-

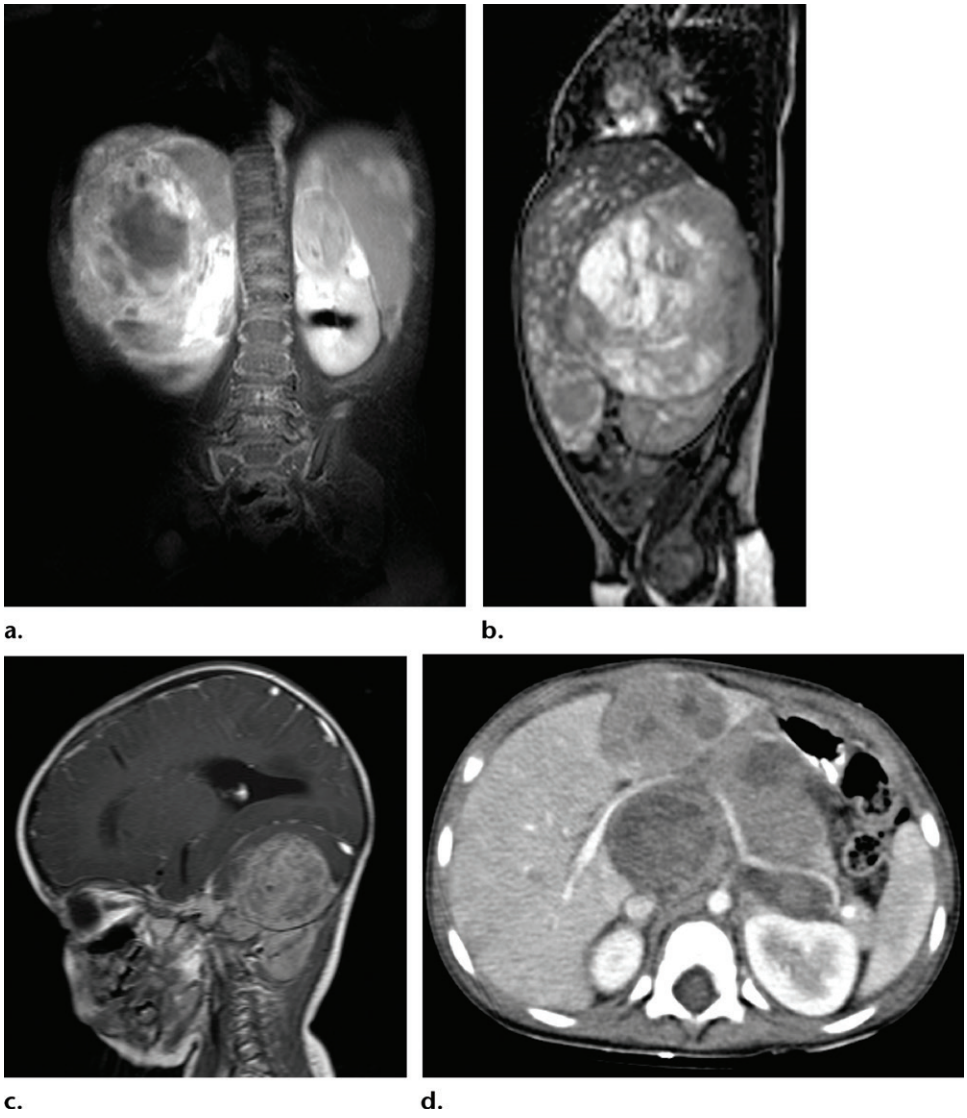


Figure 17. Asynchronous development of neuroblastoma in identical twins. **(a, b)** An abdominal mass was discovered in one of the twins at 4 months of age. Coronal contrast material–enhanced T1-weighted **(a)** and sagittal T2-weighted **(b)** MR images show bilateral adrenal masses, left thoracic paraspinal masses, and multiple hepatic metastases. These tumors were subsequently proved to be *MYCN*-amplified neuroblastoma. **(c, d)** Obstructive hydrocephalus was detected in the other twin at 19 months of age. **(c)** Sagittal contrast-enhanced T1-weighted MR image shows a large mass emanating from the occipital bone. **(d)** Axial contrast-enhanced CT image shows a large retroperitoneal mass with metastatic lesions in the liver. Subsequent biopsy revealed *MYCN*-amplified neuroblastoma.

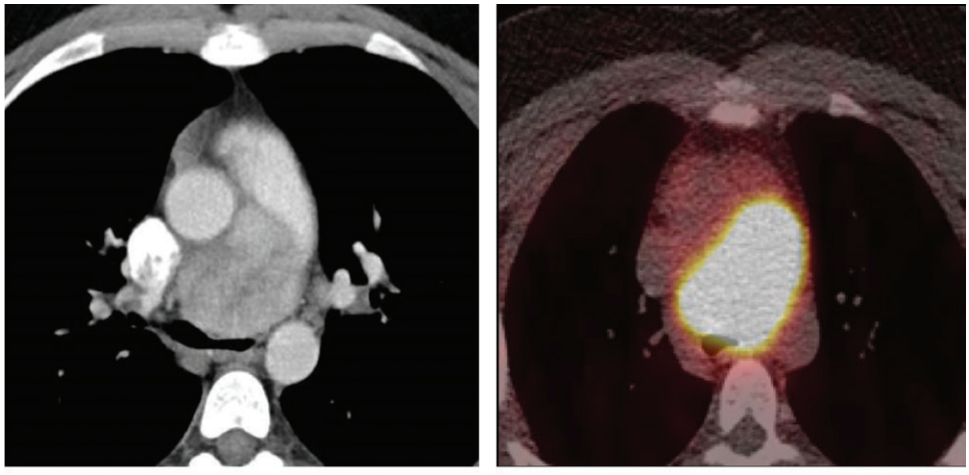
chromocytoma or paraganglioma in patients with inconclusive biochemical test results, assessment for multifocality, exclusion of metastases, and identification of tumors with somatostatin receptors for targeted radiation therapy (63).

Gallium 68 (^{68}Ga) tetraazacyclododecane tetraacetic acid somatostatin agonist imaging is the first choice for functional nuclear medicine imaging in individuals with extra-adrenal or head and neck pheochromocytomas or paragangliomas because it is associated with a high pheochromocytoma or paraganglioma detection rate (Fig 18). Identifying somatostatin receptors is also important for selecting patients for targeted molecular radiation therapy.

When the presence or absence of multiple adrenal foci is in question in a patient with sporadic or inherited pheochromocytoma (ie, patients with *NF1*, *VHL*, *RET*, or *MAX* gene mutations), the use of fluorodihydroxyphenylalanine may be advantageous because of the lack of uptake of this agent in the normal adrenal medulla. Iodine 123 (^{123}I) metaiodobenzylguanidine concentrates in tissues that express catecholamine-secreting tumors (Fig 19), so nonsecreting pheochromocytomas or paragangliomas may not be detected with this radiotracer (63).

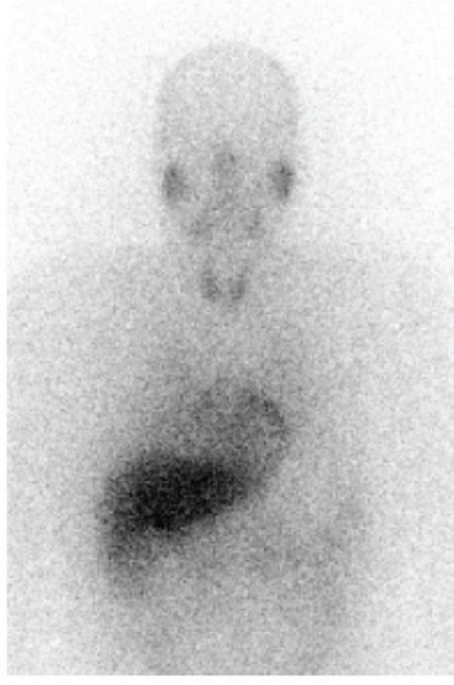
MTC and MEN Type 2 Syndromes

MTC is a rare malignancy that arises from calcitonin-producing parafollicular C cells of the thyroid



a. b.

Figure 18. Findings in a 17-year-old boy with shortness of breath. **(a)** Axial contrast-enhanced CT image shows a middle mediastinal mass, which was subsequently sampled at biopsy; pheochromocytoma or paraganglioma was revealed. **(b, c)** The mass demonstrated ^{68}Ga–somatostatin analog uptake on the axial fused PET/CT scan **(b)** but lack of iodine 123 (^{123}I)–metaiodobenzylguanidine uptake on the frontal anteroposterior static scintigram obtained 24 hours later **(c)**.



c.

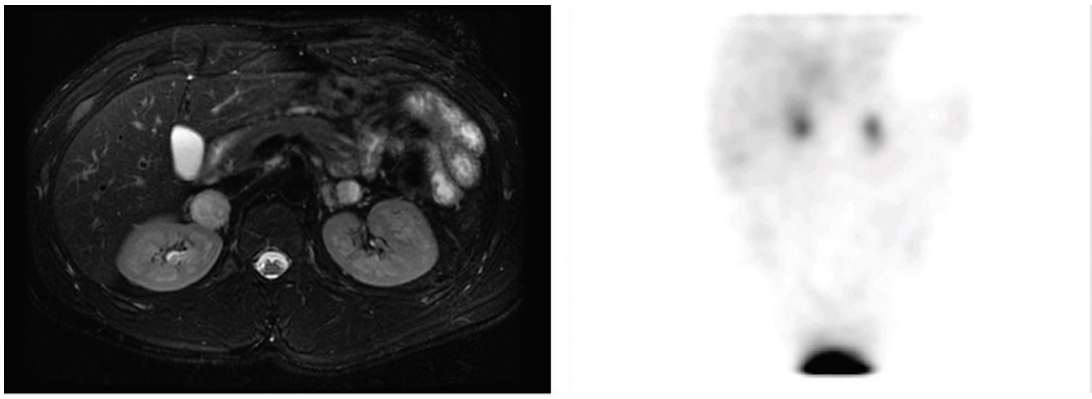
gland (cranial neural crest derivative). The thyroid gland originates from two major structures: The medial thyroid is formed by the endodermal primitive pharynx, while the lateral thyroid (containing parafollicular C cells) originates from the cranial neural crest (65,66). MTC manifests at the junction of the middle and upper thirds of the lateral lobe, which is the site of most parafollicular C cells (Fig 20).

MTC represents approximately 5% of thyroid malignancies. Up to 25% of MTCs are familial and a component of MEN type 2 (MEN 2) syndrome. There are three subsets of MEN 2 syndrome: MEN 2A, MEN 2B, and familial MTC (64).

MTC in association with MEN 2 syndromes is often bilateral and multicentric, while sporadic MTCs are usually unilateral (67). In addition, the ages of persons when MTC develops are quite different among the MEN 2 syndrome subtypes. Familial MTC typically manifests in individuals in their 40s and 50s, whereas MEN 2A typically manifests in persons during late adolescence or early adulthood. Individuals with MEN 2B often develop MTC during infancy or early childhood (67). MEN 2A accounts for 90%–95% of childhood MTC cases, while MEN 2B is associated with the most aggressive clinical manifestations, with rapidly growing bilateral multicentric tumors and metastasis manifesting during the early ages (39).

All MEN 2 syndromes are characterized by MTC but involve different associated disorders. MEN 2A is associated with pheochromocytomas (10%–60%) and hyperparathyroidism (10%–30%). MEN 2B is associated with pheochromocytomas (50%), marfanoid habitus (100%), intestinal ganglioneuromatosis (60%–90%), and mucosal neuromas (60%–90%). Persons with familial MTC rarely have associated disorders.

Gain-of-function mutations in the RET proto-oncogene have been found to be responsible in almost all cases of MTC in individuals with MEN 2 syndromes. During embryogenesis, the *RET* gene is expressed in the neural crest, urogenital precursors, and adrenal medulla. Later in the person's life, it is expressed in the central and peripheral nervous systems and the endocrine system (41). The *RET* gene has a pivotal role in regulating the proliferation, migration, and differentiation of NCCs (68).



a. b.

Figure 19. von Hippel–Lindau syndrome and hypertension in a 17-year-old boy. **(a)** Axial T2-weighted MR image shows bilateral adrenal masses. **(b)** Frontal anteroposterior static ^{123}I-metaiodobenzylguanidine scintigram shows bilateral pheochromocytomas.

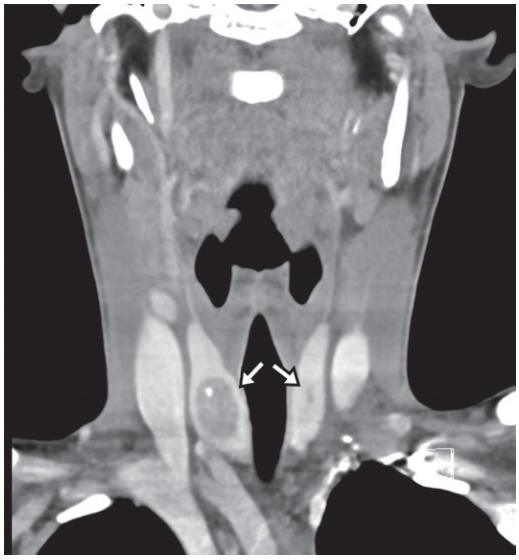


Figure 20. MEN 2B syndrome and bilateral MTC in a 14-year-old boy with marfanoid body habitus and buccal neuromas. Coronal contrast-enhanced CT image of the neck shows bilateral thyroid masses (arrows) arising from the lateral thyroid, consistent with MTC.

While gain-of-function mutations have been implicated in familial MTC, it is interesting that loss-of-function mutations in the *RET* gene have been found in a higher percentage of familial Hirschsprung disease cases than in sporadic cases. Although there is a high correlation between *RET* gene mutations and MTC, the lower rates of *RET* mutations with Hirschsprung disease may suggest additional gene involvement or incomplete penetrance with variable risk of Hirschsprung disease development (39). Analysis of the *RET* gene allows confirmation of the diagnosis of MEN 2B by facilitating identification of the causal germline mutation. Once the diagnosis of MEN 2B is made, prophylactic total thyroidectomy is recommended for infants in their 1st year of life (69).

Combined Dysgenetic and Neoplastic NCPs

While sporadic neuroblastoma, pheochromocytoma and paraganglioma, and MTC are considered neoplastic NCPs, familial cases and those associated with other syndromes should be considered both dysgenetic and neoplastic. This is because they have a germline mutation (dysgenetic) that results in neoplasms. Combined dysgenetic and neoplastic NCPs (already discussed) include familial pheochromocytoma and paraganglioma syndromes, familial neuroblastoma syndromes, and MEN 2 syndromes.

Neurocutaneous Syndromes

Neurocutaneous syndromes, previously known as phakomatoses, are a diverse group of diseases traditionally characterized by the coexistence of abnormalities of the brain and skin. Despite the traditional view that neurocutaneous syndromes are diseases of the ectoderm, many of them involve tissues of mesodermal and/or endodermal origin (12). Bolande's initial description of NCPs included NF1, and in recent years there have been suggestions to include other neurocutaneous syndromes (1,19).

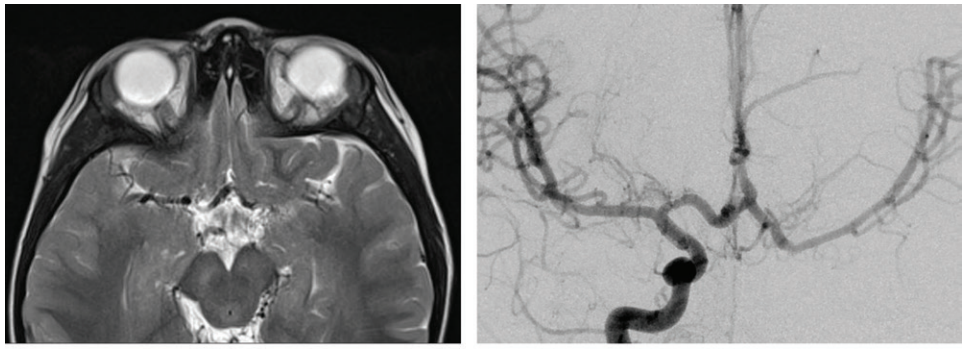
Many neurocutaneous syndromes share common features, including abnormal angiogenesis and abnormalities involving NCC derivatives such as peripheral and autonomic neuronal tissues, chromaffin cells, adipose tissue, and melanocytes. Pigmentation abnormality sometimes follows lines of Blashko, which are presumed migratory pathways of embryonic cells of the skin, including melanocyte precursors. The concept of NCP provides a unifying embryologic basis for these multisystemic diseases (Table 4) (12).

NF1 is one of the most common and well-described neurocutaneous syndromes, with a prevalence of one in 4000 individuals (70). It is a

Table 4: Neurocutaneous Syndromes and Related Features

NCS	Associated Gene(s)	NCC-related NCS	Non–NCC-related NCS	NCS Associated with Other NCPs
NF1	*NF1**	Pigmentation anomalies (café-au-lait spots, Lisch nodules) Facial dysmorphisms Vascular dysplasias (moyamoya syndrome, renovascular hypertension) Neurofibroma, glioma, schwannoma, MPNST	UBO GBM Breast cancers Leukemias	Neuroblastoma Pheochromocytomas and paragangliomas
NF2	*NF2**	Meningiomas, schwannomas	Ependymomas	…
TS	*TSC1** *TSC2**	Pigmentation anomalies (hypomelanotic macules, shagreen patches) Angiofibromas, angiomyolipomas, fibromas	Hamartomas SEGA	…
SW	…	Vascular malformations of skin and meninges	…	…
VHL	*VHL*	Angiomatosis Hemangioblastomas Pheochromocytomas and paragangliomas	Renal cell carcinomas Pancreatic cysts ELST	…
WS	*PAX3* *SOX10*	Hypopigmentation (iris, hair, skin, cochlear) Facial dysmorphisms	…	Hirschsprung disease Neuroblastoma

Note.—ELST = endolymphatic sac tumor, GBM = glioblastoma multiforme, MPNST = malignant peripheral neural sheath tumor, NCS = neurocutaneous syndrome, NF2 = neurofibromatosis type 2, SEGA = subependymal giant cell astrocytoma, SW = Sturge-Weber syndrome, TS = tuberous sclerosis, UBO = unidentified bright objects, VHL = von Hippel–Lindau syndrome, WS = Waardenburg syndrome.
**NF1, NF2, TSC1,* and *TSC2* are tumor suppressor genes.



a. **b.**

Figure 21. NF1 and moyamoya syndrome in an 8-year-old girl. Axial T2-weighted MR image **(a)** and conventional angiogram **(b)** show termination of flow in the left internal carotid artery, with reconstitution of flow in the left anterior artery and middle cerebral artery through the anterior communicator and small perforators of the diencephalon (moyamoya vascularity).

complex autosomal dominant disorder caused by germline mutations in the *NF1* tumor suppressor gene on chromosome 17 (70). NF1 involves dermal neurofibromas and melanocytic abnormalities (eg, café-au-lait macules, skinfold freckling, and Lisch nodules), both of which are considered abnormalities related to NCC development.

Other tumors of neural crest origin that are associated with NF1 include pheochromocytomas, schwannomas, and malignant peripheral nerve sheath tumors. The cerebral vascular dysplasia seen with NF1 may also be explained by developmental abnormalities of the cerebral vascular smooth muscle, another neural crest derivative (Fig 21) (71). Deactivation of the tumor suppressor function of the *NF1* gene may explain the development of tumors of non–neural crest origin, including optic gliomas and glioblastomas (72).

The concept of NCPs helps radiologists understand the common thread connecting seemingly unrelated manifestations of NF1 and, in turn, develop imaging strategies for the initial evaluation and follow-up surveillance of this disease. Targeted molecular therapies have been attempted in NF1 animal models for the treatment of plexiform neurofibromas, with promising findings for gene editing, gene replacement, and immunomodulation techniques in the future (73).

Conclusion

The neural crest and its derivatives have an essential role in the pathogenesis of many birth defects, malformation syndromes, and neoplasms. By having a basic understanding of neural crest development, clinicians can identify many seemingly unrelated diseases as NCPs.

The plasticity and multipotency of NCCs may lead to promising opportunities for future treatment of various NCPs, with cell reprogramming and stem cell manipulation. Adult NCCs also may have potential to be used as endogenous progenitors for healing and regeneration (73,74).

NCPs often affect multiple organ systems within a single individual and tend to occur in families with significant phenotypic variability. They are also frequently associated with the development of neoplasms. Radiologists are positioned to have significant roles in the diagnosis and evaluation of NCPs and any associated subclinical lesions and the planning for follow-up and treatment. Radiologists can and should be important members of a multidisciplinary management team for lifelong care of patients with NCPs.

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