

# PHACE Syndrome Handbook

A guide for parents & physicians

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# PHACE Syndrome Handbook: A Guide for Parents and Physicians

Sponsored by Pediatric Dermatology at the Medical College of Wisconsin and the Birthmarks and Vascular Anomalies Center at Children's Hospital of Wisconsin

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**\*\*Note: Sections are listed by how common each abnormality is observed in PHACE syndrome. This does not mean every child diagnosed with PHACE will have each of the listed abnormalities. Our goal is to educate parents and physicians about all the possible abnormalities observed in PHACE syndrome.**

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# Introduction to PHACE Syndrome

## What is PHACE syndrome?

A *syndrome* is defined as a recognizable pattern of medical conditions that occur together. **PHACE syndrome** is a disorder characterized by large infantile hemangiomas of the face, scalp and neck associated with developmental defects of the brain, blood vessels, eyes, heart, and chest wall.

## History of PHACE syndrome

PHACE syndrome is a relatively newly discovered entity, and was first described in 1996 by an astute physician who recognized a pattern of problems in babies with large facial hemangiomas. Dr. Ilona Frieden and colleagues published a medical paper detailing 5 babies with large facial hemangiomas and anomalies of the brain, aortic arch, eye, and arteries. Frieden created the term **PHACE**, which is an acronym (a word formed from the first letters of the several words in the name) which refers to **P**osterior fossa anomalies, **H**emangioma, **A**rterial lesions, **C**ardiac abnormalities/**C**oarctation of the aorta, and **E**ye anomalies. A physician in Spain also noted a similar constellation of findings (Pascual Castroviejo type II syndrome).

In that same paper, Frieden also reviewed previously published papers that described similar conditions. We believe that many children had PHACE syndrome in the past but were unrecognized or were misdiagnosed as another syndrome. Even though it has been recognized for almost 15 years, in medical terms this is still

considered a very new syndrome and we have much more to learn. Since this report, many more cases of PHACE syndrome have been identified; with every child diagnosed with PHACE syndrome, we discover more about this condition.

Every child diagnosed with PHACE syndrome has a different combination of abnormalities associated with the syndrome. Not every affected child has all of the same symptoms, and there is a spectrum of severity. In most cases, there is no history of PHACE syndrome or similar medical conditions in the family. For reasons we do not understand, girls are more likely to get PHACE syndrome when compared to boys, but the severity of the disease does not seem to be worse in either sex. At this point, little is known about what problems may occur as children with PHACE syndrome get older. The cause of PHACE syndrome remains unknown. However, nationwide research efforts are beginning to provide valuable information about PHACE syndrome with the goal of improving clinical care for these children.

### **How common is PHACE syndrome?**

Although relatively uncommon, over 400 cases of PHACE syndrome have been reported in the medical literature. This number, however, is most likely an underrepresentation of the true number of PHACE syndrome cases due to a variety of reasons. First, the reported cases found in the literature often have the most severe abnormalities associated with PHACE syndrome. Thus, children who have a more mild form of PHACE syndrome may not be reported in medical journals. Second, some children that were previously misdiagnosed with other diseases, most notably Sturge-Weber Syndrome, may actually have PHACE syndrome. As understanding and recognition of PHACE syndrome increases, the reported number of patients diagnosed with the syndrome is expected to increase.

### **How is PHACE syndrome diagnosed?**

The identification of PHACE syndrome is made by a *clinical diagnosis* - this means there is no one sign or symptom that will indicate a diagnosis of PHACE syndrome. Currently, there is no blood test or genetic test for PHACE syndrome. Physicians use a combination of signs and symptoms called *diagnostic criteria* to make the diagnosis (see Tables 1 and 2). Most children with PHACE syndrome have a large hemangioma on the face, scalp, or neck. One study found that 31% of children with large infantile hemangiomas on the face or scalp have PHACE syndrome. Rarely, children with large hemangiomas of the arm and/or trunk may also have PHACE syndrome. Children with a large segmental hemangioma (see Infantile Hemangioma section) of the head and neck should undergo a thorough evaluation, especially of the brain, heart, blood vessels and eyes. If a child is at risk for PHACE syndrome, certain tests and examinations should be considered.



## What tests need to be done to diagnose PHACE syndrome?

It is recommended that infants at risk for PHACE syndrome with large ( $>24 \text{ cm}^2$ ) hemangiomas of the face or scalp undergo several tests to evaluate their brain, neck, chest, heart and eyes. These tests may include:

- A history and physical examination is a comprehensive evaluation of the patient by a physician. During this examination the physician gathers information about the infant's past medical problems, problems experienced during the pregnancy, and an overview of medical conditions that may or may not run in the family. Additionally, the physician will perform a physical examination of the infant. The information gathered will help to guide future consultations and examinations as well as treatment planning. This initial assessment will supply information to the physician that provides guidance on further consultations and studies.
- An ophthalmic (eye) exam is performed by an **ophthalmologist** (eye doctor) to check vision and the health of the eyes. During this examination the ophthalmologist may check eye movements, reaction to light, and use an ophthalmoscope to check the deep and surface anatomy of the eye. This examination may be used to look for the eye abnormalities of PHACE syndrome. For more information about ophthalmic exams, please refer to the Eye Abnormalities section.
- An **echocardiogram** (echo) is an ultrasound test that uses sound waves to create a moving picture of the heart and large blood vessels arising from the heart. This test is similar to the sonogram or ultrasound used to observe a baby while pregnant. This picture is much more detailed than an x-ray image and involves no radiation exposure. An echocardiogram allows doctors to diagnose, evaluate, and monitor the heart and aortic abnormalities associated with PHACE syndrome. For more information about heart abnormalities or echocardiograms, please refer to the Congenital Heart Abnormalities section.
- A **magnetic resonance imaging** (MRI) and **magnetic resonance angiogram** (MRA) of the head and neck should be ordered if PHACE syndrome is suspected. These tests can provide important information needed to diagnose certain conditions associated with PHACE syndrome such as abnormal arterial blood vessels and abnormalities of the brain. Both MRI and MRA use a magnetic field and a computer to provide a detailed image of the body and internal organs. An MRI of the brain provides detailed pictures that allow doctors to look for findings of PHACE syndrome. An MRA of the head, neck, and chest provides detailed pictures of the arterial blood vessels through the use of a contrast agent. An intravenous (IV) line needs to be inserted so that the contrast material can be injected into the bloodstream. The same machine is used for both an MRI and an MRA and in most cases these tests are done at the same time. There is no radiation exposure during an MRI or MRA. Because slight movements may interfere with the quality of the images, infants and young children may need to be sedated so they do not move. For more information



about brain abnormalities, please refer to the Intracranial Hemangiomas, Cerebrovascular Abnormalities, Brain Abnormalities, and Neurologic Abnormalities sections.

- Occasionally, a **computed tomography angiogram** (CTA) may be used to look at blood vessels of the brain, neck, and chest. This is a special type of CT scan that uses intravenous (IV) dye to highlight the body's blood vessels.

### **What are the diagnostic criteria for PHACE syndrome?**

The diagnosis of PHACE syndrome is made by using a combination of major and minor criteria. *Major criteria* are findings that are common in PHACE syndrome but rare in other medical conditions. *Minor criteria* are findings that are seen in PHACE syndrome but can also be found in other conditions. There are additional features of PHACE syndrome that are not included in the diagnostic criteria but are still very important to the health and management of children with PHACE syndrome. We cover these additional features in the last few chapters.

Affected children are classified into two categories, definite PHACE syndrome and possible PHACE syndrome, based on the nature and number of criteria met. *Definite PHACE syndrome* requires the presence of a characteristic segmental hemangioma greater than 5 cm in diameter on the face (or scalp) plus one of the major criterion or two minor criteria listed in Table 1. *Possible PHACE syndrome* can be diagnosed in one of three different combinations: a) Facial hemangioma greater than 5 cm in diameter plus 1 minor criterion; b) hemangioma of the neck or upper torso plus 1 major criterion or 2 minor criteria; or c) no hemangioma plus 2 major criteria. Note that more than one anomaly in one organ system (for example, two heart conditions) only counts for one criterion.



**Table 1:** Diagnostic criteria for PHACE syndrome

<b>Organ System</b>	<b>Major Criteria</b>	<b>Minor Criteria</b>
Cerebrovascular	<ul style="list-style-type: none"> <li>• Anomaly of major cerebral arteries</li> <li>• Dysplasia of the large cerebral arteries</li> <li>• Arterial stenosis or occlusion with or without moyamoya collaterals</li> <li>• Absence or moderate-severe hypoplasia of the large cerebral arteries</li> <li>• Aberrant origin or course of the large cerebral arteries</li> <li>• Persistent trigeminal artery</li> <li>• Saccular aneurysms of any cerebral arteries</li> </ul>	<ul style="list-style-type: none"> <li>• Persistent embryonic artery other than trigeminal artery</li> <li>• Proatlantal intersegmental artery (types 1 and 2)</li> <li>• Primitive hypoglossal artery</li> <li>• Primitive otic artery</li> </ul>
Structural Brain	<ul style="list-style-type: none"> <li>• Posterior fossa anomaly</li> <li>• Dandy-Walker complex or unilateral/bilateral cerebellar hypoplasia/dysplasia</li> </ul>	<ul style="list-style-type: none"> <li>• Enhancing extra-axial lesion with features consistent with intracranial hemangioma</li> <li>• Midline anomaly</li> <li>• Neuronal migration disorder</li> </ul>
Cardiovascular	<ul style="list-style-type: none"> <li>• Aortic arch anomaly</li> <li>• Coarctation of aorta</li> <li>• Dysplasia</li> <li>• Aneurysm</li> <li>• Aberrant origin of the subclavian artery with or without a vascular ring</li> </ul>	<ul style="list-style-type: none"> <li>• Ventricular septal defect</li> <li>• Right aortic arch (double aortic arch)</li> </ul>
Ocular	<ul style="list-style-type: none"> <li>• Posterior segment abnormality</li> <li>• Persistent fetal vasculature (Persistent hyperplastic primary vitreous)</li> <li>• Retinal vascular anomalies</li> <li>• Morning glory disc anomaly</li> <li>• Optic nerve hypoplasia</li> <li>• Peripapillary staphyloma</li> <li>• Coloboma</li> </ul>	<ul style="list-style-type: none"> <li>• Anterior segment abnormality</li> <li>• Sclerocornea</li> <li>• Cataract</li> <li>• Coloboma</li> <li>• Microphthalmia</li> </ul>
Ventral or Midline	<ul style="list-style-type: none"> <li>• Sternal defect</li> <li>• Sternal cleft</li> <li>• Supraumbilical raphe</li> </ul>	<ul style="list-style-type: none"> <li>• Hypopituitarism</li> <li>• Ectopic thyroid</li> </ul>

**Table 2:** Categories of PHACE syndrome

<b>Definite PHACE Syndrome</b>		
Facial Hemangioma > 5 cm PLUS 1 Major OR 2 Minor Criteria		
<b>Possible PHACE syndrome</b>		
Facial Hemangioma > 5 cm PLUS 1 Minor Criteria	Hemangioma of the Neck or Upper Torso PLUS 1 Major OR 2 Minor Criteria	2 Major Criteria without Hemangioma

**What causes PHACE syndrome?**

Although there is research in progress to determine the cause of PHACE syndrome, still very little is known about the development and natural history of this syndrome. The abnormalities associated with this syndrome are thought to be due to errors that occur very early during development, but why the errors occur is unknown. There may be a genetic component involved and studies are underway to investigate this idea. No familial cases have been identified to date.

**How many children will have PHACE syndrome within a family?**

No cases of PHACE syndrome have been identified in the same family. However, if there is a suspicion of PHACE syndrome in any child, it is always best to visit a physician.

**What doctors should evaluate a baby suspected to have PHACE syndrome?**

If a child has been diagnosed with PHACE syndrome, we recommend that the child be evaluated by a *multidisciplinary team* (doctors from many different specialties) of physicians to ensure that all aspects of the child's health are evaluated and treated. These doctors should have experience in treating infants and children with PHACE syndrome. Depending on the child, a pediatrician, pediatric dermatologist, hematologist/oncologist, ophthalmologist, radiologist, neurologist, cardiac surgeon, plastic surgeon, general surgeon, geneticist, cardiologist, and otolaryngologist may need to be involved. This network of physicians will be critical in providing the most comprehensive care and support that the child may need in the future.



## Infantile Hemangiomas

### What is an infantile hemangioma?

An **infantile hemangioma** is a common type of birthmark. In the past, terms such as strawberry mark or strawberry birthmark were used for infantile hemangiomas. The word *birthmark* is a general term used to describe abnormalities of the skin. A baby can develop birthmarks either before being born or soon after birth. Birthmark is a broad term and should not be used as a specific diagnosis as there are many types of birthmarks.

Infantile hemangiomas are unlike other birthmarks, in that they grow and change greatly during the first months of life. Infantile hemangiomas are made up of *endothelial cells* (cells that line the inside of blood vessels), which multiply at a quicker rate than normal. Hence, it is referred to as a *benign* (non-cancerous) tumor. Generally, infantile hemangiomas are absent or subtle at birth and gradually appear during the first few weeks of life. Most skin hemangiomas are seen by 6 months of age. During the natural course of a hemangioma, the birthmark reaches a point of maximum growth and then begins to shrink and disappear.

Rarely, hemangiomas can develop in the internal organs of the body. For example, they can grow in the liver, airway, gastrointestinal tract, and sometimes in other organs.

### What does a hemangioma look like?

Hemangiomas can occur anywhere on the skin, but most often are found on the skin of the head or neck. They may be located in the outer layers of the skin (superficial hemangioma) or under the skin in the fat (deep hemangioma). A mixed hemangioma has both superficial and deep components to it. The color of a hemangioma varies depending on whether it is superficial, deep, or mixed. Most hemangiomas are round or oval in shape, but larger lesions may follow the shape of the affected body part. The size of hemangiomas is also variable, ranging from very small (1 mm) to very large (20 cm or larger). Every hemangioma differs in how fast it grows and how long it grows before it stops.

A **superficial hemangioma** is a birthmark made up of blood vessel cells that is near the outer layer of the skin. It will appear bright red to purple in color, and the surface may look uneven. Often, this benign tumor is called a 'strawberry birthmark' because of its appearance.



Figure 1:  
A superficial hemangioma

Figure 2: A deep hemangioma



A **deep hemangioma** is a birthmark made up of blood vessel cells that is located deeper in the skin or in the fat layers. A deep hemangioma can be bluish in color, or could have a normal skin color. Often deep hemangiomas may not be seen or felt until a baby is 4-6 months old, after it has entered the *proliferative* (major growth) phase and becomes *protuberant* (bulges out from the surrounding surface).

**Mixed hemangiomas** are the most common type of hemangioma. These hemangiomas have both superficial and deep components.

### What is the most common hemangioma seen in PHACE syndrome?

Typically, the hemangiomas that are seen in PHACE syndrome cover a large area of the skin on the head or neck (greater than 5 cm). As a result, the term **segmental hemangioma** has been used to describe the appearance of hemangiomas that are associated with PHACE syndrome. Segmental hemangiomas often extend over a broad area, rather than a focal point as seen with the previous examples. These segmental hemangiomas tend to be greater than 5 cm in diameter and most often span one side of the face and neck. In newborns, segmental hemangiomas can be *telangiectatic* (broken blood vessel-like), or flat cherry-red patches. Segmental hemangiomas of the scalp, face, or neck are present in more than 95% of patients with PHACE syndrome.

Figure 3: A segmental hemangioma



### How is a hemangioma diagnosed and what specialist should I see?

In most cases, the diagnosis of a hemangioma can be made by the child's primary doctor, but sometimes vascular anomalies specialists may be needed to ensure the accuracy of the diagnosis. Segmental hemangiomas can sometimes be mistaken for port-wine stains, a type of flat red birthmark, so the expertise of a pediatric dermatologist may be needed for more unusual cases.

### What are some of the complications involved with hemangiomas?

- **Interference with function:** As a hemangioma grows it can interfere with the normal functions of the region where it is located. This is most often observed around the eye (see Eye Abnormalities section). A hemangioma near the eye may obstruct the infant's vision, which may cause an irreversible loss of sight. As a result, it is important to closely monitor hemangiomas near the eyelids. Other hemangiomas that may need urgent treatment are those in the airway (see Airway Compression section), in the brain (see Intracranial Hemangiomas section), in the diaper area, and around the mouth or nose.

- **Ulceration:** The skin over the hemangioma can break down. The skin may appear raw or shiny and might develop a scab. Ulcerations can be very painful for the child, which can lead to irritability and difficulty feeding or sleeping. They also increase the risk of infection and scarring. Hemangiomas that are located on the mouth, nose, ear, and diaper region carry a higher risk of ulceration. Ulcerations heal slowly and treatment might be recommended to speed up this process and to prevent infection and scarring.
- **Bleeding:** The blood vessels that make up hemangiomas are not normal. When hemangiomas bleed, they tend to bleed rapidly, but only for a short period of time. The bleeding should stop with gentle, direct pressure for fifteen minutes. If bleeding returns or does not stop with pressure, the child's doctor should be contacted promptly.

### How are hemangiomas treated?

In general, most infantile hemangiomas are not treated because they shrink over time and disappear completely on their own. The decision to treat a hemangioma is determined by the age of the patient and the size, location, and growth rate of the hemangioma. Hemangiomas that are located in areas that can threaten health (airway or liver) or normal development (brain, ear canal, or eye), and those hemangiomas that are potentially disfiguring (face) are treated more quickly and aggressively than hemangiomas that pose less of a risk. Children with PHACE syndrome often have large hemangiomas and are more likely to have complications that require treatment. The doctor will discuss whether treatment is needed and what treatment is best for the child. ***There are no medications currently approved by the Federal Drug Administration (FDA) to treat infantile hemangiomas.*** This is due in part to the expense of conducting drug approval studies. All medications currently used by physicians for this purpose are considered “off label,” in that they have not been “labeled” by the FDA to use for this diagnosis. The pros and cons of using medications in babies with PHACE syndrome must be carefully considered by physicians with expertise in both treating hemangiomas and PHACE syndrome.

Treatment options include:

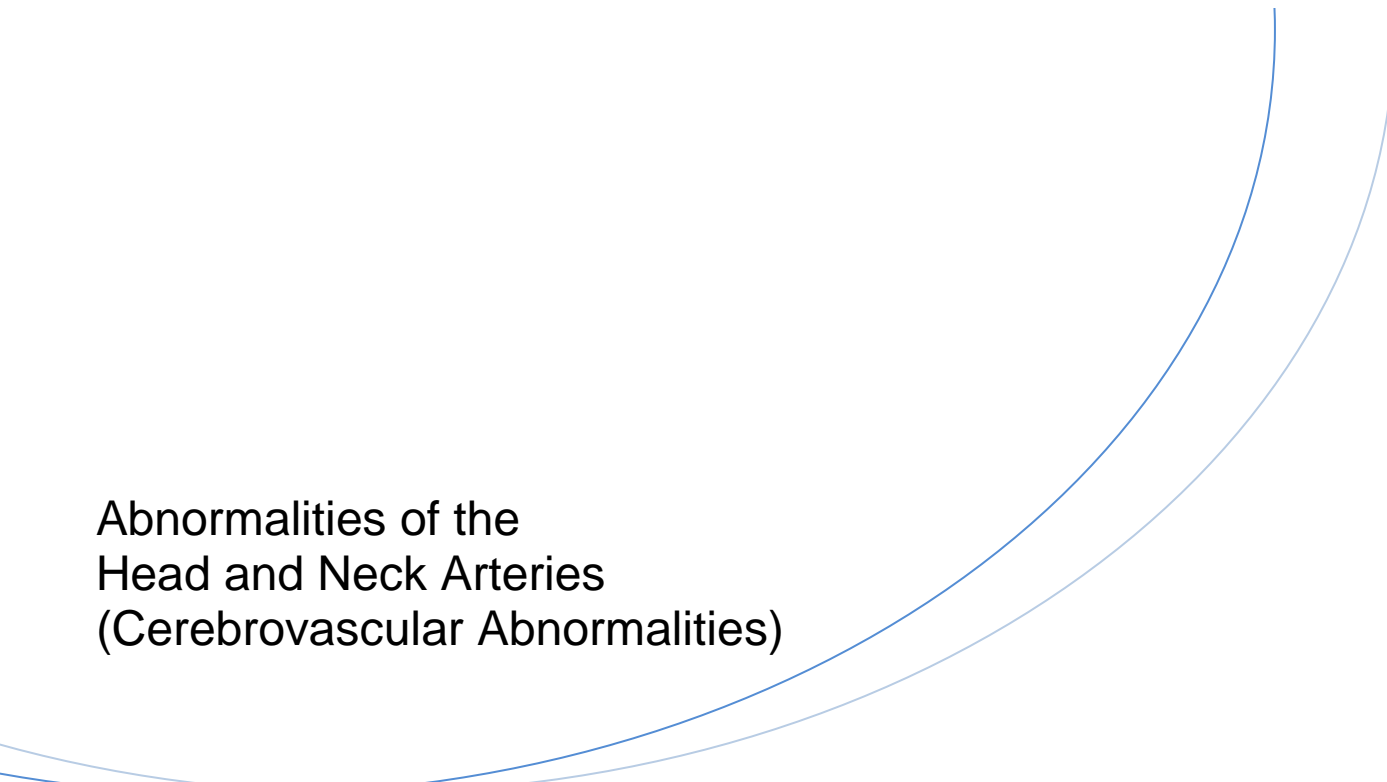
- **Observation** is used for hemangiomas that are growing slowly or not threatening function of the eye, ear, or airway. Even though most hemangiomas will not require an oral medication or surgery, we believe that all hemangiomas should be monitored closely, especially during infancy. Hemangiomas undergo the most rapid period of growth during the first months of life and should be closely monitored during this period for potential complications.
- **Oral (taken by mouth) systemic corticosteroids** (such as prednisone, prednisolone, Orapred) have become a mainstay in the treatment of hemangiomas, yet their mechanism of action is not well understood. Oral steroids are used to control or stop the growth of hemangiomas. They are only used during the growth

period, and in most cases do not shrink the hemangioma, but instead control its growth. The duration of treatment ranges from a few weeks to many months depending on the child's age, the indications for treatment, and the growth characteristics of the hemangioma. Despite a list of potential side effects including irritability, gastrointestinal upset, immunosuppression, hypertension, and growth retardation, most treated infants do tolerate the medications well. By closely monitoring the patient, parents and physicians can usually minimize the chances of any side effects from this treatment.

- Intralesional (injected) corticosteroids are injected through a small needle directly into the hemangioma and are effective for small, localized skin hemangiomas.
- Topical (applied directly to the skin) corticosteroids are also effective in controlling the growth of small superficial hemangiomas, particularly on the eyelid and around the mouth.
- Surgical excision (removal) is used most frequently to reconstruct scars or to remove *fibrofatty tissue* (the excess skin left behind when a hemangioma resolves). Early excision is an option in selected cases. Such cases include small hemangiomas with complications that are located in areas where surgical scars will be less noticeable, when a residual abnormality is inevitable or the hemangioma threatens life or bodily function, and when drug therapy is not effective or well tolerated. The hemangiomas observed in PHACE syndrome tend to be large and involve the nose, lip, and eye; therefore, surgical excision is not possible in most cases. The pros and cons of a surgical approach must be carefully considered since the scar from surgery may be worse than leaving a hemangioma to go away on its own. Generally, re-evaluation is recommended at about age 4 to assess how much residual hemangioma is present and to consider surgery for scarring or slowly *regressing* (shrinking) hemangiomas.
- Laser therapy has also been used to treat hemangiomas. Because of its limited depth of penetration, the flash-lamp pulsed dye laser works well for superficial hemangiomas but has no impact on deeper or thicker hemangiomas. It is most often used to improve the telangiectasia (broken blood vessels) after regression of the hemangiomas and may be effective in treating ulcerated hemangiomas to decrease pain and encourage healing. Using the flash-lamp pulsed dye laser in babies less than 6 months of age with PHACE syndrome has been shown to have an increased risk of scarring. Continuous-wave lasers such as the argon, neodymium:yttrium-aluminum-garnet (Nd:YAG), and potassium titanyl phosphate (KTP) have also been used but require greater physician expertise and training and have a greater risk of scarring.
- Vincristine is a medication that is used to treat a variety of tumors. Recently, it has been successfully used to treat hemangiomas that threaten important functions such as vision or breathing. This medication is given as an injection into a *central venous line* (special type of IV line) on a weekly basis.



- Propranolol (Inderal) is a beta-blocker medication that has been used for many years to treat high blood pressure. Recently, it was recognized that propranolol may work in the treatment of hemangiomas. This medication must be used with caution because it can cause a drop in blood pressure, heart rate, or body temperature. It also may cause a drop in blood sugar if the infant does not eat regularly. Careful observation is necessary, especially in children with PHACE syndrome who have cardiac, aortic arch, or arterial abnormalities. This medication is given by mouth two to three times a day.
- Topical timolol gel is a beta-blocker medication that can be applied directly to the hemangioma two times a day. This is often used to treat small superficial hemangiomas.
- Regranex gel (becaplermin) is a topical medication used once a day to heal ulcerations, but it does not slow the growth of hemangiomas. It is a fairly new medication that the FDA has approved to treat diabetic ulcers in adults. It is very expensive and may not be covered by insurance without more information from a doctor.



## Abnormalities of the Head and Neck Arteries (Cerebrovascular Abnormalities)

### What are cerebrovascular abnormalities?

A **cerebrovascular abnormality** is an abnormal blood vessel of the brain. In the case of PHACE syndrome, patients can have abnormalities of the arteries that carry blood to the brain either in the head (**cerebral**) or neck (**cervical**). The arteries in the chest, neck, and brain are the most frequent arteries found to be abnormal in PHACE syndrome. These blood vessels can have abnormal shapes, sizes, or paths through the neck and head.

### What are the arteries of the chest, neck and brain?

Blood is carried to the brain through blood vessels called arteries. *Arteries* are defined as blood vessels that carry blood away from the heart to deliver oxygenated blood to the tissues of the body. Blood is initially pumped from the heart into the **aorta**, the body's biggest artery. It then travels up to the brain through smaller branching arteries. The first branch off of the aortic arch is the **innominate artery** (also called the **brachiocephalic artery**), which provides blood to the right side of the head and neck. The innominate artery immediately branches into the right **subclavian artery** and right **common carotid artery**. The second branch off of the aorta is the left common carotid artery. The third branch off of the aorta is the left subclavian artery.

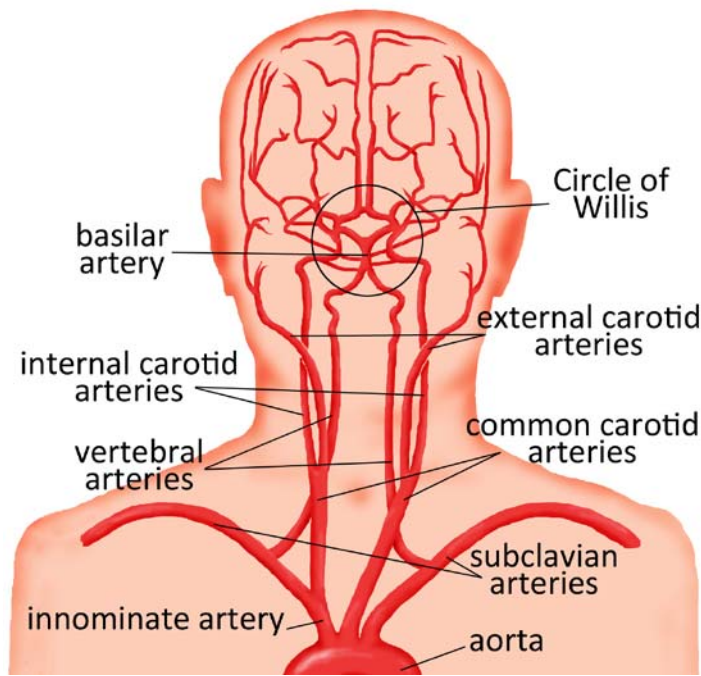


Figure 4: Major arteries of the head, neck, and brain

Both the right and left common carotid arteries divide into the external and internal carotid arteries at the carotid bifurcation. The **internal carotid arteries** carry blood directly to the front and middle parts of the brain while the **external carotid artery** carries blood to the face and scalp.

Both of the subclavian arteries carry blood mainly to the arms, but they also carry blood to the brain through branching of the vertebral arteries. The **vertebral arteries** arise from the subclavian arteries and carry blood up toward the brain along the spinal column. These arteries fuse together and form the **basilar artery** which supplies blood to the back of the brain.

The blood travelling from the back of the head through the basilar artery and the blood travelling from the front of the head through the internal carotid arteries meet at the **Circle of Willis**. The Circle of Willis is a circular group of arteries that provides a connection for blood flowing from the back to the front of the body.

### Why is the Circle of Willis important?

The Circle of Willis is very important because it helps to make sure oxygen and nutrient-rich blood reaches all areas of the brain. In a way, it is considered the “back up” system for blood supply to the brain and serves the same function as a highway bypass, allowing for an alternate route if there is a traffic jam in the normal route. For example, if there is a blockage in the left internal carotid artery and blood is not able to reach the front of the left side of the brain, blood can move from the right internal carotid artery through the anterior communicating artery to the left side of the brain. In this example, if the Circle of Willis did not exist, there would be no way for blood to reach the back of the brain. The brain is the body’s most vital organ, and it must have a constant supply of blood to work properly. If the blood supply to the brain is interrupted, a stroke can result. When nerve cells in the brain are damaged or die, the functions they control, such as movement, speech and learning may be affected. The effects of a stroke on a child’s ability to function depend on the area of the brain which is damaged; the symptoms may be temporary or permanent (see Neurologic Abnormalities section).

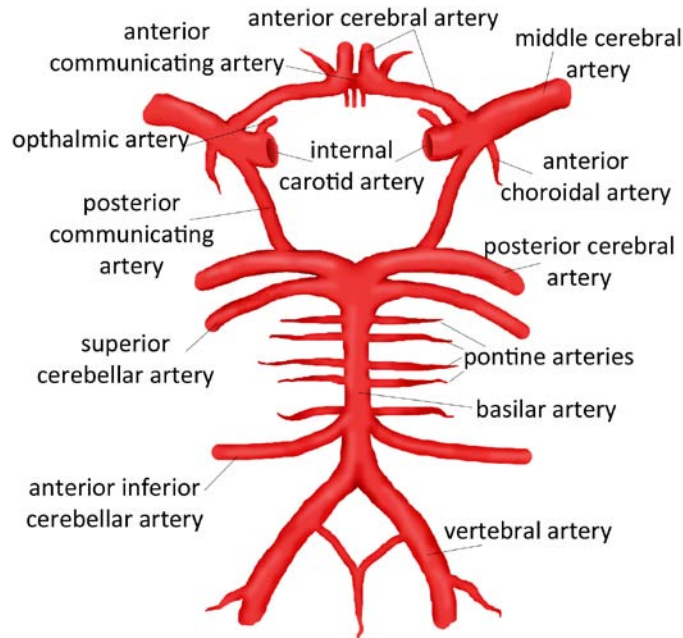


Figure 5: Detail of the Circle of Willis

### What cerebrovascular abnormalities are seen in children with PHACE syndrome?

The blood vessels of the head and neck in children with PHACE syndrome can be abnormal. The five main types of abnormalities are:

- **Dysgenesis:** This describes an artery that has abnormal looping, kinking, elongation, or dilation.
- **Narrowing:** The width of the arteries is smaller than normal.
- **Non-visualization:** This means that there is an absence of a normal artery because it did not form, or it is not seen on an MRI/MRA because blockage prevents the flow of contrast through the vessel.
- **Abnormal course or origin:** This means that the artery does not deliver blood to where it normally does or that it branches off (begins) from an abnormal point
- **Persistent fetal arteries:** This is when blood vessels that usually disappear after birth are still present.

### **What arteries are most commonly affected?**

The internal carotid artery is the most frequently involved abnormal artery. According to a recent study, anomalies of the internal carotid artery are present in approximately 75% of PHACE syndrome patients who have cerebrovascular abnormalities. The abnormal artery is most often located on the same side as the facial hemangioma.

### **What persistent fetal arteries are seen in PHACE syndrome?**

The trigeminal artery is the most common persistent fetal artery seen in approximately 12-19% of PHACE syndrome patients. Persistent hypoglossal (3%) and stapedia (1.5%) arteries can also be observed. These fetal arteries are normally open and functional for a short period of time during fetal development. The trigeminal artery and hypoglossal arteries connect the blood vessels of the front and back of the head and neck. The stapedia artery connects the internal carotid and external carotid arteries. Children with persistent fetal arteries may be at an increased risk for an **aneurysm** (balloon-like growth) or *dilation* (widening) at the point where the persistent fetal vessel joins a normal artery.

### **How common are abnormal arteries of the head and neck seen in children with PHACE syndrome?**

Besides the hemangioma on the skin, abnormal blood vessels of the head and neck are the most common abnormality seen in children with PHACE syndrome. It has been estimated that greater than 80% of children with PHACE syndrome have at least one abnormal artery in their neck or head, and many have several abnormal arteries in this region.

Currently, the exact reason why PHACE syndrome patients have abnormal arteries of the head and neck is not known, but researchers have some ideas. Physicians believe that there are defects in the formation of the internal carotid arteries during fetal development that causes decreased blood flow. Due to the lack of blood flow, the vessels that would normally branch off the internal carotid artery and supply the brain do not form correctly. It is believed that this is why some fetal remain - to allow flow to parts of the brain that otherwise wouldn't receive adequate blood flow.

### **How is a cerebrovascular abnormality diagnosed?**

A cerebrovascular abnormality cannot be determined by physical exam, so special radiologic imaging is needed. An MRI/MRA of the head and neck, a computed tomography angiogram, or an angiogram may be used to diagnose the underlying blood vessel abnormalities. Depending on what the imaging studies show, repeat imaging may be needed at a later date.

### **What are some of the complications involved with having abnormal arteries?**

Some PHACE syndrome patients with abnormal arteries of the head and neck may have an increased risk of stroke, seizures, and motor or language developmental delays as compared to children with normally formed arteries. A **stroke** is the loss of brain function due to disturbance in blood supply to the brain. The risk of stroke in children with PHACE syndrome with abnormal arteries is unknown but it is believed to be very rare. A recent literature review of all PHACE syndrome patients reported in the literature (a little more than 400) found 22 cases of stroke. Most of these patients had narrowing or non-visualization of at least one great cerebral artery and almost three-quarters of the patients had these changes in 2 or more great cerebral arteries. A little more than half of these patients had abnormalities of the aortic arch. In this group, the most common signs of stroke were seizures and hemiparesis. The cause of stroke is complicated, but the highest risk of stroke seems to be the combination of greater than one narrow cerebral artery, a problem with the blood flow in the Circle of Willis and aortic arch anomalies. Physicians and researchers are still working to develop a systematic way of identifying which PHACE syndrome patients are at an increased risk of stroke so they can be closely followed and managed.

### **How can parents tell if their child is having a stroke or seizure?**

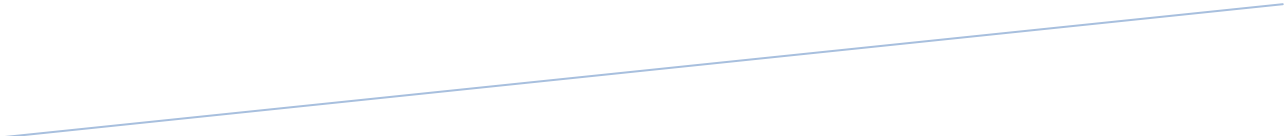
Symptoms of a stroke or seizure could include abnormal eye movements, tremor, decreased body tone (limpness), head bobbing, limb or body weakness, inability to move the limbs or body, headache, or absence of breathing (see Neurologic Abnormalities section).

### **Are there any treatments to prevent strokes or seizures?**

Currently there are no guidelines to treat PHACE syndrome patients who have had strokes or seizures, or who are believed to be at an increased risk for either. Children who have had a stroke or seizure, or who are believed to be at an increased risk for these may be treated by their physician with aspirin.

### **What research is being done regarding cerebrovascular abnormalities in PHACE syndrome patients?**

A multidisciplinary team of physicians have done research to evaluate the MRA/MRI of PHACE syndrome patients with cerebrovascular abnormalities to determine if these abnormalities stay the same or change over time. With the information obtained in this study, physicians hope to be able to establish guidelines for when patients need MRA/MRI and to establish the best treatment to limit stroke risk.



## Structural Brain Abnormalities

### What are the structures of the brain and what do they do?

The brain acts as the control center of the central nervous system (CNS), which consists of the brain and spinal cord. The brain regulates many bodily functions including movement, thought, speech, vision, respiration, planning, emotions, and memory by receiving and analyzing sensory input (information) from the body and external environment and then sending out signals to control and communicate with other regions of the brain and body. PHACE syndrome has been associated with abnormalities of several different areas of the brain. One area in particular is the space at the base of the skull which contains the brainstem and cerebellum, called the **posterior fossa**.

- Hindbrain: This is an area of the brain that includes the cerebellum, medulla oblongata and pons. This brain region plays a central role in the execution of involuntary or *autonomic* behaviors (actions you do not need to think about doing, such as blinking and temperature regulation).
  - Spinal Cord: Think of this as the main highway system that provides a link between the brain and the body, carrying information back and forth between the two.
  - Medulla Oblongata: The area of the brain that helps to control autonomic (involuntary) functions such as breathing, digestion, and heart rate.
  - Pons: The area of the brain that plays an important role in consciousness and sleep.



- **Cerebellum:** Traditionally viewed as the area of the brain which controls complex motor functions. It also plays a key role in selecting the appropriate behavior or action in a given situation (like choosing the correct sequence of movements when reaching for a cup, or selecting the appropriate emotional or social response at a funeral versus a birthday). Additionally, the cerebellum plays a role in the more complex features of human language (such as determining how two words are related, or deciding if a sentence is grammatically correct). Finally, the ability of the cerebellum to change behavior in response to rapid changes or cues is an important feature of executive functions like planning, reasoning, working memory, and verbal fluency.
  
- **Cerebral cortex:** This is what most people think of when describing the brain. The cerebral cortex is divided into two *hemispheres* (halves), the right and left. The right hemisphere controls the left side of the body, and vice versa.
  - **Frontal lobe:** Located at the front of the brain, this is the area of the brain associated with complex reasoning, planning, behavior regulation, personality, decision making, movement and expressive language abilities.
  - **Parietal lobe:** This area of the brain plays a key role in the processing of sensation (pain and touch), orientation to objects in our environment, movement, speech and visuospatial perception.
  - **Temporal lobe:** The area of the brain associated with auditory (sound) processing, emotion, memory, language organization and comprehension (understanding), and retrieval of information from memory storage.
  - **Occipital lobe:** Located at the back of the brain, this area controls the processing, integration and interpretation of visual information.

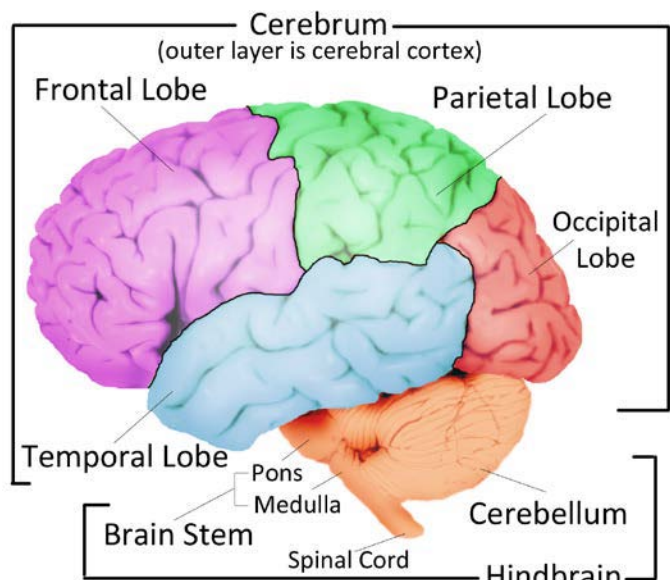


Figure 6: Major structures of the brain associated with PHACE syndrome

### What structural brain abnormalities are seen in children with PHACE syndrome?

- **Dandy-Walker complex** is a developmental malformation of the brain involving the cerebellum and the fluid-filled spaces around it. It includes an enlargement of the fourth *ventricle* (a small channel that allows fluid to flow freely between the upper and lower areas of the brain and spinal cord), a partial or complete absence of the area of the brain between the two cerebellar hemispheres (*cerebellar vermis*), and cyst formation near the internal base of the skull. *Hydrocephalus* (an enlargement of the fluid-filled spaces surrounding the brain which may lead to increased pressure inside the skull and increased head size) may also be present.
- Cerebellar hypoplasia or atrophy is a neurological condition in which the cerebellum is not fully developed or is smaller than usual. The terms hypoplasia, atrophy, and dysgenesis are often used interchangeably. In patients with PHACE syndrome, the hypoplasia is usually only in one half of the cerebellum.
- Subependymal and arachnoid cysts are found in the brain as sacs of cerebrospinal fluid surrounded by a membrane.
- Hypoplasia or agenesis of cerebrum is a developmental abnormality characterized by the absence or reduced size of a cerebral hemisphere. This abnormality may be related to a stroke occurring during fetal development.
- Hypoplasia or agenesis of the corpus callosum is a developmental abnormality in which there is a partial or complete absence of the *corpus callosum* (a structure that connects the left and right sides of the brain). This defect can occur alone or in combination with other brain defects such as Dandy-Walker complex.
- Hypoplasia or agenesis of the septum pellucidum is a developmental abnormality in which the *septum pellucidum* (a thin membrane found in the middle of the brain) is absent or reduced in size.
- Hypoplasia or agenesis of the vermis is a developmental abnormality characterized by a partial or complete absence of the *cerebellar vermis* (the middle portion of the cerebellum located between the two cerebellar hemispheres which plays a role in the body's position control). This abnormality often occurs as a component of the Dandy-Walker complex.
- Polymicrogyria is characterized by a greater than normal amount of folding (*gyri*) of the surface of the cerebral hemispheres.

- Cortical dysplasia occurs when *neurons* (nerve cells) do not migrate to the proper location on the *cerebral cortex* (outermost layer of the cerebrum).
- Absent pituitary or partially empty sella turcica. The pituitary is a small endocrine gland (see Endocrine Abnormalities section) located at the base of the brain. It produces several hormones which are important in controlling growth, thyroid function, salt and water balance in the body, and sex hormones. The *sella turcica* is the bony structure in the base of the skull which holds the pituitary gland. The pituitary gland can be underdeveloped or completely absent in children with PHACE syndrome.

### **How common are structural brain abnormalities in PHACE syndrome?**

Recent studies have reported that 42-52% of children with PHACE syndrome have a structural brain malformation. Patients with structural malformations almost always have at least one associated abnormality of the cerebral vasculature (blood vessels of the brain). Cerebellar hypoplasia is the most common structural brain malformation in children with PHACE syndrome.

### **What are some of the complications involved with having structural brain abnormalities?**

Generally, cerebellar abnormalities are shown by having symptoms of *hypotonia* (see Neurologic Abnormalities section), *disequilibrium* (loss of balance during activities such as walking or sitting), and *dyssynergia* (loss of more complex coordinated motor activities). Dyssynergia can result in a variety of symptoms including slurred speech, difficulty coordinating voluntary movements, difficulty stopping a movement once it has started, difficulty in performing rapidly alternating movements, and lack of coordinated eye movements.

In addition to these motor symptoms, structural brain abnormalities of the cerebellum in particular can result in a many neuropsychological symptoms (see Neurologic Abnormalities section).

### **What tests may be needed to diagnose structural brain abnormalities?**

Brain abnormalities cannot be diagnosed by a physical exam, so an MRI or computed tomography (CT) is used to diagnose structural brain abnormalities.

### **What specialists may be involved in a child's care for brain anomalies?**

Children with neurologic components of PHACE syndrome may have a care team including a neurosurgeon, neurologist, neuroradiologist, dermatologist, physical therapist, occupational therapist, speech therapist, and other medical professionals.

### **Useful resources for parents and families:**

National Institute of Neurological Disorders and Stroke: <http://www.ninds.nih.gov>

## Neurologic Abnormalities

### What is the neurologic system?

*Neurology* is a medical specialty concerned with studying and treating disorders of the neurologic (nervous) system. The neurologic system includes the brain, spinal cord, and all the nerves. It regulates the body's many functions including movement, thought, speech, and vision. Physicians who specialize in neurology are called **neurologists**.

### What neurologic abnormalities have been seen in children with PHACE syndrome?

Many neurologic abnormalities have been seen in patients with PHACE syndrome. We are just beginning to understand all of the issues associated with PHACE syndrome, and further research will help to better define the problem areas. Listed below are some examples:

Seizures  
Developmental delay  
Mental retardation  
Neuropsychological deficits  
Language delay

Stroke – see Cerebrovascular  
Abnormalities section  
Hemiparesis  
Hypotonia  
Tremor

Cranial nerve weakness  
Poor attention/concentration  
Opisthotonus  
Migraine headache  
Cyclic vomiting syndrome  
Hearing loss

### **What are seizures?**

The nervous system communicates by sending electrical signals within the brain and between the brain and the nerves in the body. A **seizure** occurs when a part of the brain sends an abnormal burst of electrical signals which temporarily interrupts the brain's normal function. When children have repeated seizures that are not associated with a specific cause, the condition is called **epilepsy**. If the brain has either a structural abnormality or was injured during a stroke, the child may be at a greater risk for developing seizures.

Symptoms vary depending on the type of seizure the child experiences. Symptoms may include staring, jerking movements, stiffening of the body, loss of consciousness, difficulty breathing, loss of bowel or bladder control, appearing confused, not responding to noise or words, or head nodding.

### **How are seizures diagnosed and treated?**

Seizures can be diagnosed by history and physical examination. An **electroencephalogram** (EEG) can be a useful test. It is a non-invasive test in which the electrical activity of the brain is recorded to evaluate for abnormal activity.

The treatment choice varies depending on the type of seizures the child experiences. The goal of seizure treatment is to stop or decrease seizure frequency without harming the child's normal growth and development. Medications are often used to control seizures. There are many different medications available to treat specific types of seizures. If seizure control is not working with medications, there are other treatment options.

### **What is developmental delay?**

Developmental delay is when a child's development lags behind what is considered normal for their age; in other words, he or she does not reach their developmental milestones at the expected times. In children with PHACE syndrome, the developmental delay may be due to a structural brain abnormality or brain damage from strokes or seizures. Developmental delays can occur in gross motor function (sitting, crawling, walking, drawing), fine motor function (holding a pencil) or language (speaking, reading).

### **How is developmental delay diagnosed and treated?**

When parents notice that their child seems to be slow to learn to perform certain skills such as rolling over, sitting up, crawling, walking, or talking, they should bring this to the attention of their child's pediatrician. Developmental delay may also be noticed by the pediatrician during well-child visits. Depending on the child's deficits, he or she may be evaluated further by a neurologist, neuropsychologist, speech therapist, or other experts in child development to investigate potential causes for their delay and better characterize the child's unique needs. Treatment is directed toward each child's individual needs and varies depending on his or her

developmental delays. Children with developmental delays may benefit from occupational therapy, physical therapy, or speech therapy interventions.

### **What is mental retardation?**

Children with mental retardation have below-average intellectual function and also lack skills necessary for daily living. Unlike developmental delay (where children do reach their milestones eventually), children with mental retardation have permanent deficiencies in certain areas. Neuropsychological testing provides a formal assessment of a child's *cognitive functioning* (processing of thoughts and information). This testing can determine whether a child has any cognitive deficits and provide formal assessment of deficits in daily living skills. Additionally, this testing may be helpful in determining the child's special educational needs. Children with mental retardation may benefit from speech or occupational therapy and may need special educational classes.

### **What are neuropsychological deficits?**

A neuropsychological deficit can be described as an area of *cognition* (thinking) in which the child is behind other children of the same age and education. Neuropsychological deficits can happen in any area of thinking including language, memory, attention, planning, reading, spelling, math, behavioral inhibition, and much more. Testing can determine whether a child has this and provide strategies for potential treatment including behavior modification, parent training, medications, speech therapy, and individualized educational plans.

### **What are stroke and hemiparesis?**

A stroke occurs when the blood supply to the brain is disrupted and the nerve cells in the area of the brain lacking blood supply are damaged and may die due to lack of oxygen-rich blood (see Cerebrovascular Abnormalities section). **Hemiparesis** is muscle weakness on one side of the body and can occur in children who have had a stroke which damaged areas of their brain that control muscles and movement. Because of the way muscle control is arranged in the brain, the weakness is seen on the opposite side of the body (*contralateral*) to where the stroke occurred in the brain. Children with hemiparesis may benefit from physical therapy, occupational therapy, and custom made braces for their legs in order to maximize their mobility.

### **What is hypotonia?**

**Hypotonia** is decreased muscle tone (limpness). Hypotonia is different than muscle weakness, but weakness may be present along with hypotonia. Hypotonia can occur throughout the whole body or be localized to muscles in a certain area. Infants with hypotonia may appear "floppy" since they have poor head and muscle control. Children with hypotonia may have delayed motor skill development, decreased strength, poor posture, drooling, swallowing difficulties, speech impairments, and hyper-flexible joints.

### **How is hypotonia diagnosed and treated?**

Patients with hypotonia should have a thorough physical exam with testing to evaluate their motor skills, balance, coordination, reflexes, sensation, and nerve function. They may also need imaging tests such as an MRI or CT scan of the brain, an EEG to measure the brain's electrical activity, or an EMG (electromyogram) to evaluate how the nerves and muscles function together. The symptoms of hypotonia can be addressed with physical, occupational, and speech therapies to improve the child's motor skills, strength, and speech.

### **What is opisthotonus?**

**Opisthotonus** is a condition in which a child's body spasms in a posture of extreme hyperextension and stiffness with their head and heels arched backwards. This posturing can be triggered by movements such as a caregiver's attempts to hold or feed the child or even by a light touch. This makes it difficult to care for the child or to place them in a car seat. This condition is most often seen in children whose brain was without oxygen for a prolonged period of time. It has also been seen in children with Dandy-Walker complex. It can be treated with muscle relaxant medications.

### **What are migraine headaches?**

A migraine headache is a type of headache characterized by certain symptoms such as light or sound sensitivity, nausea or vomiting, abdominal discomfort, or sweating. They can occur occasionally or be recurrent. The average age of onset for migraines in children is 5-8 years old, and there is often a family history of migraines. Children with PHACE syndrome appear to be at an increased risk of migraines, perhaps related to the cerebrovascular abnormalities associated with this syndrome. More research needs to be done to determine the frequency and cause of migraines in children with PHACE syndrome.

### **How are migraine headaches diagnosed and treated?**

The diagnosis of a headache is made with a careful history and physical examination. Additional tests such as blood tests, MRI, MRA, or CT scan may be performed to look for the cause of symptoms. Treatments for migraine headaches include resting in a quiet and dark environment, avoiding known triggers, stress management, dietary changes, and exercise. Medications may be prescribed by the child's physician to treat the pain (rescue medications), stop headaches in progress (abortive medications), or reduce the number of headaches (preventive medications).

### **What is cyclic vomiting syndrome?**

Cyclic vomiting syndrome (CVS) is characterized by episodes of severe nausea and vomiting that can last from hours to days. These episodes occur in cycles alternating with symptom-free periods of time. CVS is thought to be related to migraines and usually begins in childhood between the ages of 3-7. Episodes of CVS can be triggered by stress, excitement, or illness. Continued vomiting can lead to severe dehydration with symptoms

of decreased urination, increased thirst, pale skin, and fatigue. Children with these symptoms of dehydration should see a doctor immediately.

### **How is cyclic vomiting syndrome diagnosed and treated?**

It is difficult to diagnose CVS because there are no specific tests for CVS. Blood tests and X-rays may need to be done to rule out other diseases that can cause nausea and vomiting. After other conditions are ruled out, the diagnosis of CVS is based on the child's symptoms and medical history.

Vomiting episodes will eventually stop even if untreated. Children with CVS should get adequate sleep and can take medications to prevent vomiting episodes from occurring. Once an episode begins, medications can also be helpful to stop or shorten the episode and relieve symptoms. During an episode, children should rest in bed in a dark, quiet room and take in fluids and electrolytes as tolerated to rehydrate the body. If they have severe nausea and vomiting, they may need to be hospitalized and receive intravenous fluids to prevent dehydration. Data regarding the long-term outcomes in children with CVS is lacking, but many patients eventually recover. Some patients will develop migraine headaches later in life, and more than 1/3 of children with CVS have vomiting episodes as adults. These patients may need to continue with therapies throughout their life.

### **What specialists may be involved in a child's care for neurologic abnormalities?**

Children with neurologic components of PHACE syndrome may have a care team including a neurologist, neurosurgeon, radiologist, physical therapist, occupational therapist, speech therapist, dermatologist, neuropsychologist, and other medical professionals. It is important to find a neurologist with expertise in PHACE syndrome.

### **What research is being done regarding neurologic abnormalities in PHACE syndrome patients?**

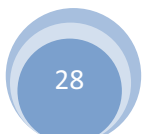
Research is currently underway to better characterize the neurologic and neuropsychological impairments seen in children with PHACE syndrome. Results from these studies will be used to allow early identification of any neurologic deficits which may be associated with PHACE syndrome and to guide treatment and therapies.

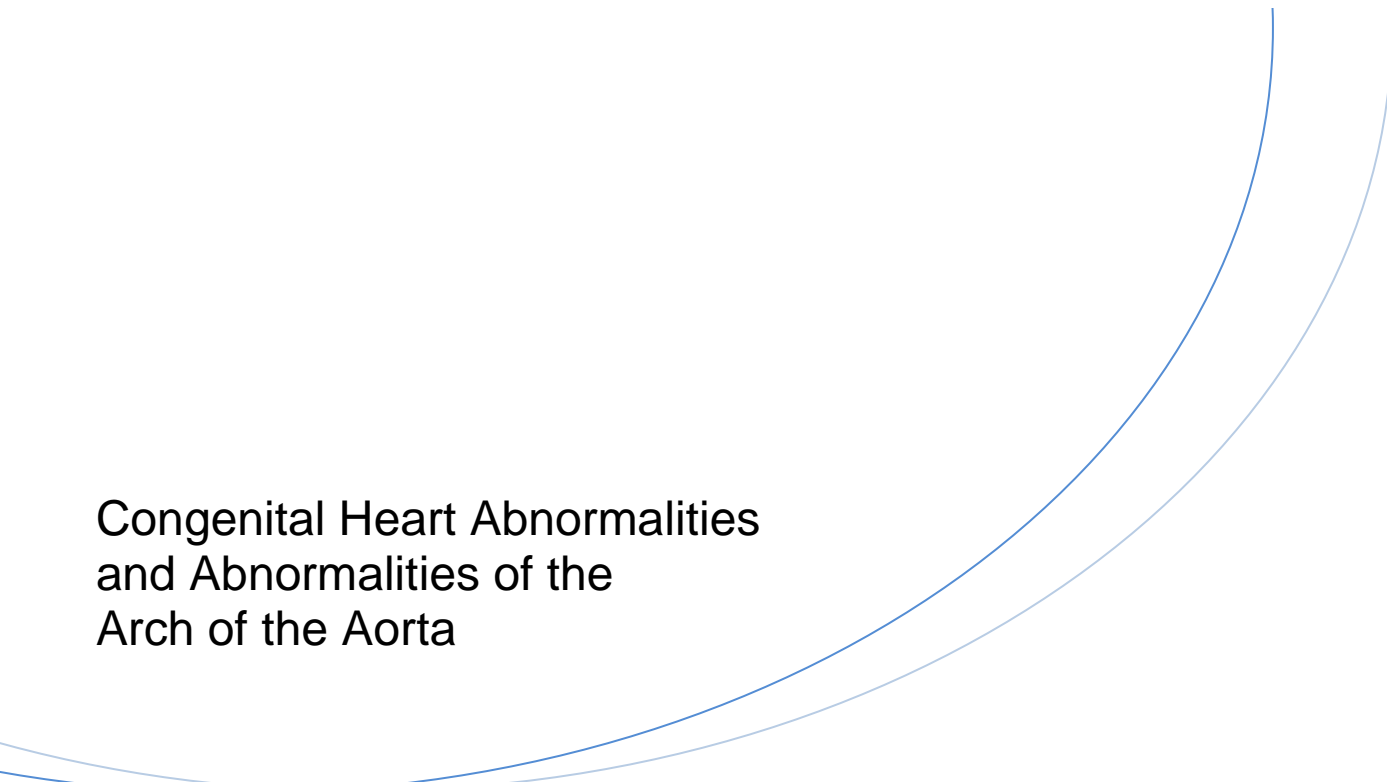
### **Useful resources for parents and families:**

National Institute of Neurological Disorders and Stroke: <http://www.ninds.nih.gov/>

Cyclic Vomiting Syndrome Association: <http://www.cvsaonline.org>







## Congenital Heart Abnormalities and Abnormalities of the Arch of the Aorta

### **What are congenital heart abnormalities?**

Congenital heart abnormalities are irregularities in the heart's structure that are present at birth as a result of faulty development of the heart. A baby's heart begins to develop a few weeks after conception. During development, structural defects can occur. These defects can involve the walls of the heart, the valves of the heart and the large arteries and veins near the heart. Congenital heart abnormalities can obstruct blood flow or redirect the normal flow of blood through and/or out of the heart.

### **What is the aortic arch and what abnormalities are seen in children with PHACE syndrome?**

When the heart is functioning normally, a large artery called the aorta carries oxygenated blood from the left ventricle of the heart to the body. It is shaped like a candy cane, with the first section moving up from the heart toward the head, called the ascending aorta. The aorta then curves in a C-shape in a region called the **aortic arch**. After the curve, the aorta becomes straight again, called the descending aorta. It moves downward toward the abdomen carrying blood to the lower part of the body. The most common defect in PHACE syndrome is **coarctation of the aorta** (narrowing of the aorta) which impairs the ability of oxygenated blood to reach the body. This occurs in 14.5% of newborns with PHACE syndrome. Usually the narrowed region is in the aortic arch and often occurs with aneurysms, or ballooning of nearby sections. Imaging of the aortic arch may appear as beads on a string, with alternating narrowed segments and ballooned segments.

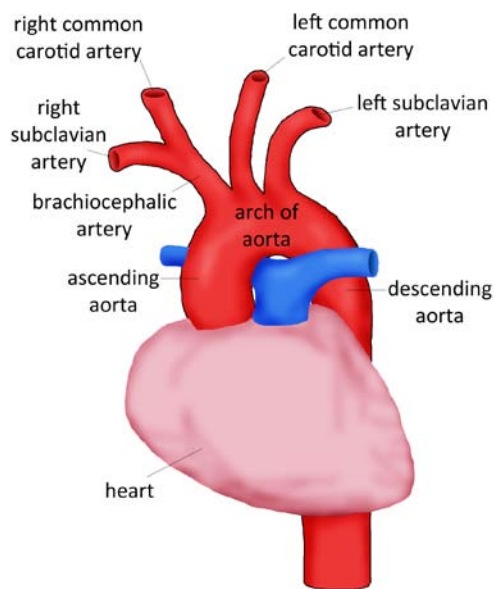


Figure 7: Normal, healthy anatomy of the aorta and its branching arteries

The aortic arch has three major vessels that supply the upper body and head with oxygenated blood. The three arteries that branch off are the innominate artery (also called brachiocephalic artery), the left common carotid artery and the left subclavian artery. In PHACE syndrome, these arteries are sometimes narrowed, misshapen or misplaced.

### How is coarctation of the aorta diagnosed?

Often, a heart or aortic arch abnormality will produce a heart murmur. A heart *murmur* is a noise caused by the turbulence of blood flowing through a narrow or malformed region. A murmur heard in the area of the aorta is often caused by coarctation of the aorta. Sometimes, coarctation can cause differences in blood pressure where the blood pressure is higher in the upper body due to increased blood flow and lower in the lower body due to decreased blood flow. This may not always be the case, especially in infants with PHACE syndrome, because of the high risk of artery malformations. If a coarctation of the aorta is suspected, the physician will order an echocardiogram or MRA of the heart and aortic arch which will show the anatomy of the aorta and evaluate for other cardiac anomalies.

### How is coarctation of the aorta treated?

The aorta may be repaired surgically in an operating room or by a cardiac catheterization procedure. The surgical repair is performed under general anesthesia. The narrowed area is either surgically removed, or made larger with the help of surrounding structures or a patch. The cardiac catheterization procedure may also be an option for treatment. During this procedure, the child is sedated and a small, thin, flexible tube (*catheter*) is inserted into a blood vessel in the groin and guided to the inside of the heart. Once the catheter is in the heart, the cardiologist will pass an inflated balloon through the narrowed section of the aorta to stretch the area open. A small device, called a stent, may also be placed in the narrowed area after the balloon dilation to keep the aorta open.

### What is an aberrant subclavian artery?

An aberrant subclavian artery, also called *arteria lusoria*, is a common form of aortic arch anomaly in the normal population (0.5%). It is much more common in children diagnosed with PHACE syndrome, occurring in as many as 15%. *Aberrant* means that it is “out of place”; so in this case, the subclavian artery is branching off the aorta “out of place”.

There are two subclavian arteries; one on the left and one on the right. Normally, the right subclavian artery arises from another artery, named the innominate artery; however, the right subclavian artery can sometimes branch off of the left aortic arch and run behind the esophagus. In most cases this is asymptomatic and does not cause problems. Occasionally, the artery puts pressure on and compresses the esophagus; this can cause problems with swallowing. If the artery is pushing on or compressing the *trachea* (wind pipe) it may cause persistent coughing or **stridor** (see Airway Compression section).

In comparison, the left subclavian artery usually arises from the arch of the aorta at a very specific point. When the left subclavian artery branches off from an atypical location on the aorta, an *aortic diverticulum* (pouch-like enlargement) at the site of attachment can occur (diverticulum of Kommerell). When this happens, a ring of blood vessels can surround the esophagus. Like the aberrant right subclavian artery, the aberrant left subclavian artery also runs behind the esophagus and pushes it towards the sternum (towards the front). The vast majority of people with aberrant subclavian arteries do not have symptoms and do not require any treatment. Mild symptoms of esophageal compression may respond to diet modifications, such as eating soft foods in small amounts.

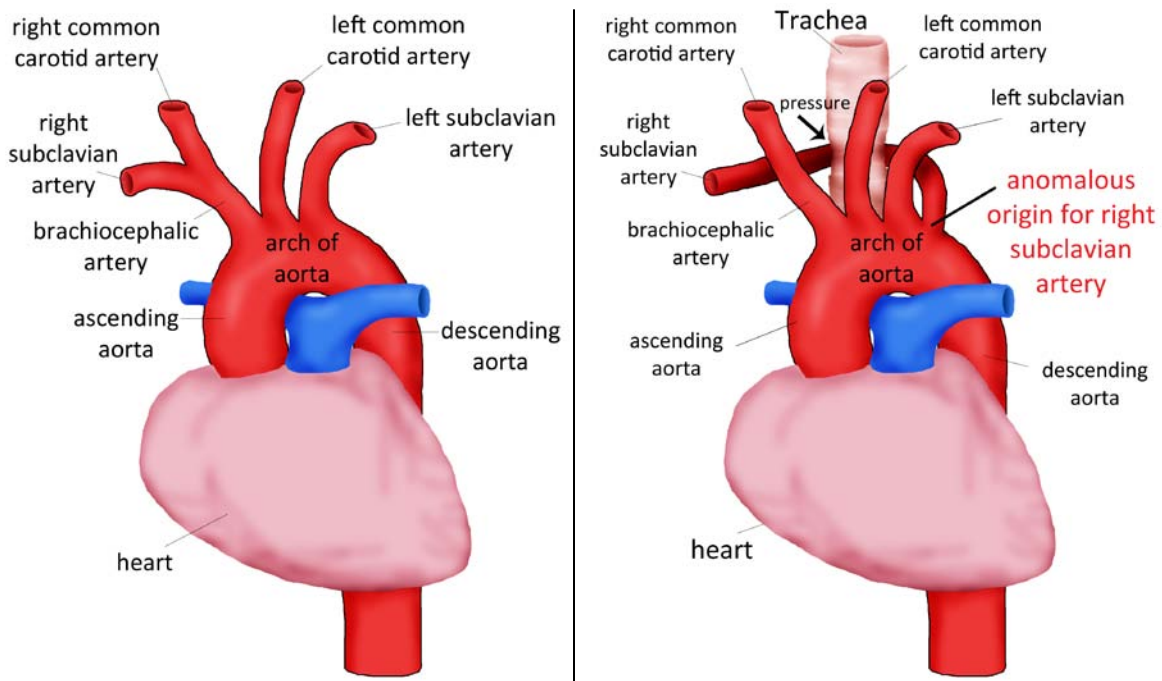


Figure 8: The diagram on the left is the normal branching configuration for the right subclavian artery. The right diagram shows an aberrant branching for the right subclavian artery coming off of the aortic arch and causing pressure as it passes behind the trachea.

### **What other congenital heart abnormalities are seen in children with PHACE syndrome?**

Blood returns from the body to the *right atrium*, the chamber on the upper right side of the heart. In the fetal heart, most of the blood flows from the right atrium to the left atrium through an opening called the *foramen ovale*. This opening normally closes at birth. If it fails to close, it is called a **patent foramen ovale** (PFO). PFOs occur in about 25% of all births and are even more common in newborns with PHACE syndrome.

A **ventricular septal defect** (VSD) is another congenital heart abnormality seen in PHACE syndrome. VSDs have been reported in 7.6% of newborns with PHACE syndrome. The *ventricular septum* is located between the left and right ventricles of the heart. It is responsible for separating the two chambers of the heart and conducting the electrical impulses of the heart. VSDs occur as imperfections in this separating tissue. These holes in the ventricular septum result in abnormal movement of blood from the left to the right ventricle, called shunting. The amount of left to right shunting of blood depends mostly upon the size of the defect.

Numerous other heart abnormalities are seen in PHACE syndrome but there is no clear pattern or consistent increase in infants with PHACE syndrome.

### **How is a ventricular septal defect diagnosed and treated?**

Most ventricular septal defects can be diagnosed on physical exam, due to their characteristic murmur. The heart can sometimes be seen or felt to be beating hard because of the extra work it is performing. Babies may continuously breathe fast or hard and have a fast heart rate if they have this condition. If a ventricular septal defect is suspected, an echocardiogram can be performed.

Most ventricular septal defects are surgically repaired by patching the opening between the ventricles. A patch of synthetic material is attached to close the abnormal opening.

### **Useful resources for parents and families:**

NHLBI Congenital Defects: [http://www.nhlbi.nih.gov/health/dci/Diseases/chd/chd\\_what.html](http://www.nhlbi.nih.gov/health/dci/Diseases/chd/chd_what.html)

Cincinnati Childrens Hospital: <http://www.cincinnatichildrens.org/health/heart-encyclopedia>

## Eye Abnormalities

### What kinds of eye problems are seen in children with PHACE syndrome?

Eye problems with PHACE syndrome are somewhat rare, but there are certain abnormalities that are seen more commonly than others. The problems most often seen in PHACE syndrome are: microphthalmia, optic nerve hypoplasia, persistent fetal vasculature, and morning glory discs.

- **Microphthalmia** is the term used when the eye is smaller than normal and has not formed correctly.
- **Optic nerve hypoplasia** refers to an underdeveloped or small optic nerve. The optic nerve conducts the images we see and transfers them to the brain as electrical impulses. This can be seen on examination by an ophthalmologist (eye doctor). Underdevelopment of the optic nerve can also be a sign that there are other brain abnormalities.
- **Persistent fetal vasculature** is where blood vessels in the retina that should disappear as the fetus develops inside the womb do not disappear. This can lead to vision problems.
- **Morning glory disc anomaly** is seen when the blood vessels that supply nutrients to the retina of the eye do not radiate from a normal central point. The optic nerve also does not develop correctly when the child

is in the womb. The result is an excess of white tissue in the back of the eye and looks like the center of the morning glory flower.

- Peripapillary staphyloma is likely due to a lengthening of the globe of the eye (eyeball), which causes a thinning and a stretching of the *sclera* (the white tissue around the iris that surrounds the eye). This allows certain layers inside of the eye to protrude through other layers.
- Coloboma is a developmental problem that happens before a child is born. A layer of tissue called the choroidal fissure does not fuse properly, resulting in an opening in the tissue. This can happen anywhere in the eye – the iris, the lens, or the tissue in the middle of the eyeball. The visual problems can be minimal to severe depending on where the incomplete fusion of tissue happened.
- Congenital third nerve palsy is a paralysis of the third cranial nerve, which affects the movement of the eyelid and eye muscles.
- Horner's syndrome is a condition where there is a disturbance in the nerves of the eye and face. The nerve dysfunction can cause *ptosis* (droopy eyelid), *myosis* (small pupil when compared to the other), and *anhidrosis* (lack of sweating) on one side of the face. This can be present at birth, or it can develop later. If a hemangioma begins pressing on a nerve or if there is a *carotid artery dissection* (a splitting of the artery that feeds the brain), Horner's syndrome can develop.
- Ptosis is an eyelid that does not open fully. In PHACE syndrome, it may be caused by a hemangioma crowding the eyelid and keeping it from opening fully. This can affect the developing vision and needs to be watched closely by a physician.
- Amblyopia, otherwise known as lazy eye, is a disorder of the visual system that is characterized by poor vision or lack of vision in an eye that is otherwise physically normal. In this condition, visual stimulation either fails to transmit or is poorly transmitted through the optic nerve to the brain for a continuous period of time. It often occurs during early childhood, resulting in poor or dim vision. Detecting the condition in early childhood increases the chance of successful treatment. Amblyopia normally affects only one eye, but it is possible to be amblyopic in both eyes. It has been estimated to affect around 1 – 5% of the normal population.

- **Proptosis** is the forward protrusion, or bulging of the eyeball. Usually, it is a sign of a severe orbital disorder, such as a tumor, inflammation, or thyroid eye disease. In PHACE syndrome, a growing hemangioma could cause the eye to be displaced.
- **Astigmatism** refers to the *cornea* (the clear tissue covering the front of the eye) being abnormally curved, causing vision to be out of focus.

### **What are the signs and symptoms of eye problems and what specialist should be seen?**

Vision is a sense that is not well developed in children at birth and it takes weeks to months for their vision to improve and sharpen. Therefore, eye problems could go unnoticed by parents for some time. However, there are certain other findings that could provide clues about potential eye development issues. One sign would be if a child has a weak eyelid (*ptosis*) or wandering eye. A wandering eye (*strabismus*) means that the eyes may be looking in different directions.

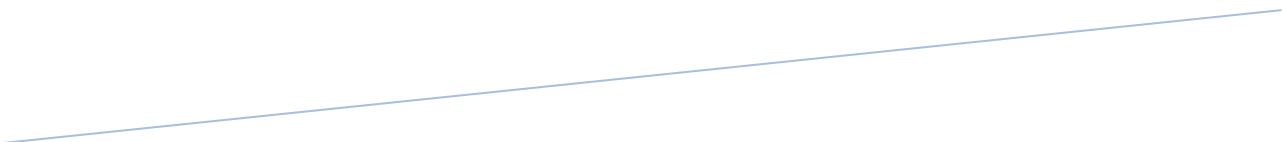
All children with PHACE syndrome should have an eye exam by an ophthalmologist who has expertise in PHACE syndrome. The ophthalmologist will make sure the child is seeing in an age-appropriate manner (an infants' vision grows sharper as they age), which can be difficult since the child cannot tell anyone how well they are seeing. The eye doctor will also check to see if both eyes are seeing equally. The eye doctor will examine the muscles of the eye, the back of the eye (the retina), and the outer parts of the eye, looking for any changes in growth or development. If a child has a hemangioma located around the eye, an ophthalmologist that has experience with hemangiomas should be seen.

The eye doctor might also use "visual evoked potentials" to test differences in visual sensation between the eyes. This is a test where the physician checks to see how well the nerves of the eye are functioning and it can be very helpful in detecting differences in the eyes.

### **How are eye abnormalities treated?**

The best treatment is prevention for certain eye problems. While there are certain developmental changes in the eye that can affect vision before the child is even born, there are certain times when treatment may be necessary to prevent a problem down the road. For example, a wandering eye is often correctable if noticed early enough in the child's growth.





## Ventral or Midline Abnormalities

### What are ventral or midline abnormalities?

A ventral or midline abnormality can be best described as a defect that occurs on the *anterior* (front) portion of a body, usually in the middle or center of the body. Numerous reports of ventral developmental defects (problems that occur before the baby is born) have been described in association with PHACE syndrome. These defects have commonly been observed in the upper portion of the sternum or can extend the entire length of sternum into the abdomen. The **sternum** is the bone in the middle of the chest wall that joins the two sides of the rib cage.

### What ventral or midline defects are seen in children with PHACE syndrome?

- **Sternal pit** is a small indentation or dimple in the skin overlying the sternum of the chest. In some cases, the skin defect can be linear extending several inches over the sternum.
- **Sternal cleft** is a birth defect where there is a groove in the sternum. The cleft may be partial or complete, meaning that the sternum is completely separated or only partially split down the center of the bone.

- Partial or complete agenesis of sternum refers to the partial or complete failure of the sternum to form. Failure of the sternum to form presents a severe problem in that it leaves the vital organs, including the heart and lungs, without the protection of the normally fused ribcage and sternum.
- **Sternal papule** is a raised bump on the skin overlying the sternum.
- **Supraumbilical raphe** is a scar-like line that extends upward from the *umbilicus* (belly button). It represents an abnormality of fusion of the layers of the skin.

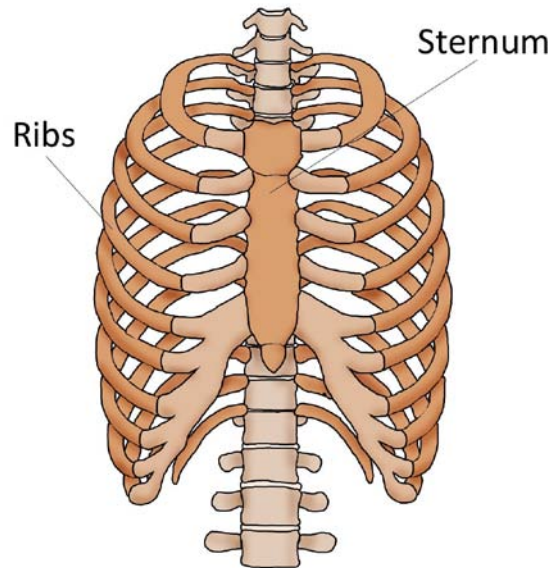


Figure 9: Location of sternum within the thoracic cage

- An omphalocele is a condition when the layers of the abdominal wall do not fuse properly and the intestines or other abdominal organs stick out. In babies with an omphalocele, the intestines are covered only by a thin layer of tissue and can be easily seen. Omphaloceles are fixed with surgical procedures.

#### How common are these defects in PHACE syndrome?

Ventral defects are not seen in all children with PHACE syndrome. The rate of occurrence depends on the type of ventral defect. Approximately 20% have a sternal defect, 9% have an umbilical raphe, and less than 2% of patients have a reported sternal papule.

#### What specialists may be involved in a child's care for ventral abnormalities?

Depending on the severity of the defect, it is best to visit the primary care physician to diagnose the problem if it has not previously been noticed. After consultation with the primary care physician, a referral to a surgeon may be recommended.

## Airway Compression

### What breathing problems can be seen in children with PHACE syndrome?

Rarely, infants with PHACE syndrome may have difficulty breathing. Three conditions seen in PHACE syndrome can cause compression (narrowing) of the airway.

- **Subglottic hemangioma:** A subglottic hemangioma is a hemangioma that is in the airway. The main difference between a *cutaneous* (skin) hemangioma and a subglottic hemangioma is the location of this blood vessel tumor. A subglottic hemangioma is in the airway just below the vocal cords, near the trachea (main breathing tube to the lungs). They are much less common than hemangiomas on the skin. Like other hemangiomas, these lesions undergo rapid growth in the first few months after birth. Infants with subglottic hemangiomas are generally born without any noticeable problems or issues for the first few weeks of life. At roughly 1 to 4 months of age, the hemangioma will begin to grow quickly and could lead to narrowing of the airway and problems with breathing.
- External compression (narrowing) of the airway from a hemangioma in the neck or chest: Compression of any part of the airway can cause breathing problems. A large hemangioma in the neck or chest over the airway can grow big enough to compress the airway. This can lead to problems getting oxygen in and out of the lungs.

- **Vascular ring:** A vascular ring is an abnormal blood vessel that pushes on, or wraps around the trachea. The arteries that deliver blood from the heart to the arms and the veins that bring blood back to the heart are very close to the trachea (see the Congenital Heart Abnormalities section). In PHACE syndrome, there can be an abnormal passage of these blood vessels that can wrap around the trachea and push on or squeeze the airway. This can cause problems with breathing, as the airway will not be as open as it should be.

### **What are the signs and symptoms of airway compression?**

Symptoms of airway compression are stridor, respiratory distress, recurrent diagnosis of “croup”, and feeding problems. Stridor is the “barking cough” that is generally associated with a child who has the viral infection croup. It is due to the narrowing of the airway. The infant could have stridor with both breathing in and out, and it could eventually get bad enough for the infant to have problems breathing and maintaining their normal oxygen levels (*respiratory distress*). Sometimes, an infant with airway compression is mistakenly diagnosed with croup. Repeated episodes of “croup” may signal airway compression. The infant may also have difficulty feeding, because they have a hard time feeding and breathing at the same time.

### **How is airway compression diagnosed and treated?**

A subglottic hemangioma is diagnosed by an **otolaryngologist** (an ear-nose-throat (ENT) physician) who can make the diagnosis with an airway examination called *endoscopy*. An endoscope is a tube with a video camera that is inserted into the infant’s nose or throat, where it can look at the airway and look for any obstruction, such as a subglottic hemangioma. Sometimes a lateral neck x-ray can be used to see if the airway is narrow.

Imaging with MRI/MRA can be used to diagnose neck and chest hemangiomas or vascular rings.

Most infants with subglottic hemangiomas need treatments such as oral steroids, vincristine, or propranolol.

### **How common is breathing issues in PHACE syndrome?**

Although subglottic hemangiomas are relatively rare, one study showed that they are seen in 24% of kids with PHACE syndrome. Features that would make a subglottic hemangioma more likely include a hemangioma on the skin in the “*beard*” *distribution* (front of the ear, jaw, chin, front of the neck, and lips). It is possible, however, to have a subglottic hemangioma, a vascular ring, or another hemangioma in the neck or chest pushing on the airway without having any hemangiomas on the skin.



## Endocrine Abnormalities

### **What is the endocrine system?**

The **endocrine system** is composed of various glands that release hormones and control vital processes in our body. For example, the endocrine system is important in regulating mood, growth and development, tissue function, metabolism, sexual function, and reproductive processes. Hormones released into the blood transfer information and instructions from a gland to other cells. Many different hormones move through the bloodstream, but each type of hormone is designed to affect only certain cells.

Hormones only bind to cells with receptors specifically designed to recognize them. A good analogy would be inserting a key into a lock, which when it fits, opens the door allowing a series of events to occur – in this case the activity of cells. If a cell does not have a receptor for the hormone, the key does not fit and there will be no effect. There can also be different receptors for the same hormone, like a master key that works on many doors, so the same hormone can have different effects on different cells.

### **What glands are involved in the endocrine system?**

A *gland* is a group of cells that produces and releases chemicals. A gland selects and removes materials from the blood, processes them, and *secretes* (releases) the finished chemical product for use somewhere in the body. The hypothalamus, pituitary, thyroid, parathyroid glands, adrenal glands, reproductive (ovaries & testes)

glands, and pancreas are the major glands that make up the endocrine system. The endocrine system is a finely tuned, interconnected system giving it the ability to have a variety of effects throughout our bodies.

### **How common are endocrine abnormalities in PHACE syndrome and which glands are generally involved?**

Only 15 instances of endocrine abnormalities in children with PHACE syndrome have been reported in the medical literature. Endocrine dysfunction has been a recent discovery in patients with PHACE syndrome, so it is unknown whether it is a rare finding or whether it has not been previously recognized. The most common glands that have been observed to show abnormalities include the pituitary and the thyroid.

Endocrine dysfunction associated with the pituitary gland is called **hypopituitarism**. Hypopituitarism is a condition in which the pituitary gland does not produce normal amounts of some or all of its hormones. Because the pituitary releases many hormones that act on other glands of the body, hypopituitarism can lead to low levels of multiple hormones. The most common hormone deficiencies in PHACE syndrome are growth hormone deficiencies, hypogonadism (low levels of sex hormones), and *diabetes insipidus* (a condition in which the kidneys are unable to conserve water).

**Hypothyroidism** is a thyroid dysfunction in which the thyroid does not make enough of its hormone. In PHACE syndrome, this condition often occurs because the thyroid gland did not move to its proper location during development. In the literature, this condition is referred to as an *ectopic thyroid gland*.

### **What are the signs and symptoms of an endocrine abnormality?**

Due to the wide range of hormone functions, a number of signs and symptoms can occur. In recent cases, the most noticeable observation seen among PHACE syndrome patients has been growth deficiencies including both height and weight. Signs of hypothyroidism to watch for include weakness, fatigue, cold upon touch, and weight gain.

### **How are endocrine abnormalities diagnosed and treated?**

If endocrine abnormalities are suspected, a physician can order blood work to check hormone levels. Depending on the endocrine dysfunction that is occurring, hormone replacement therapy is available. For example, in PHACE syndrome children with growth deficiencies, growth hormone may sometimes be given. Thyroid replacement therapy in hypothyroidism cases has also been successful.

If concerns arise about a child's endocrine system, they should first be discussed with the primary care physician. A referral to an endocrinologist for further evaluation may be necessary.

## Auditory Abnormalities

### What is the auditory system?

The auditory system performs the functions of hearing. The sense of hearing is a fine-tuned, intricate process. A sound wave is collected by the outer ear and sent through the middle ear into the inner ear where auditory hair cells are located. Once auditory hair cells in the inner ear are stimulated via sound waves, an electrical signal is generated and transmitted from these hair cells to the auditory nerve (also called cranial nerve VIII). From the auditory nerve, this signal is finally sent to the brain and subsequently processed. Hearing loss may be present if a part of the outer, middle, inner ear or auditory nerve is damaged or missing.

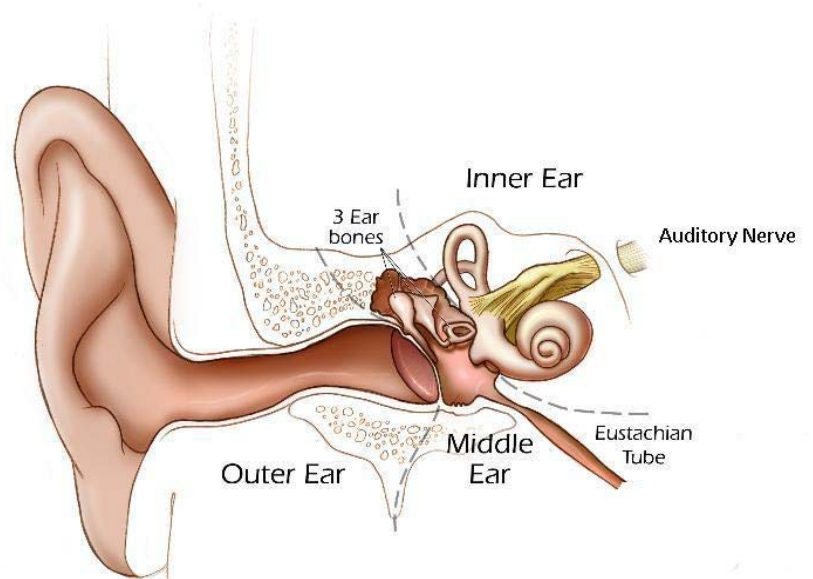


Figure 10: Diagram of the auditory system



### **What hearing abnormalities can be seen in children with PHACE syndrome?**

Hearing loss is a relatively new finding associated with PHACE syndrome. The hearing loss is most often *unilateral* (on one side) and *ipsilateral* (the same side) to the hemangioma located on a child's face. Radiologic imaging studies have attributed this hearing loss in PHACE syndrome to intracranial hemangiomas affecting various auditory structures (see Intracranial Hemangioma section).

The 3 types of hearing loss associated with PHACE syndrome are conductive, sensorineural and mixed hearing loss.

- **Conductive hearing loss** occurs when sound is not conducted efficiently through the outer ear canal to the eardrum and the tiny bones, or ossicles, of the middle ear. The most common in PHACE syndrome is an intracranial hemangioma that occludes the *Eustachian tube* (part of the middle ear). Conductive hearing loss usually involves a reduction in sound level or loss of the ability to hear faint sounds.
- **Sensorineural hearing loss** occurs when there is damage to the inner ear or to the nerve pathways from the inner ear to the brain. An intracranial hemangioma that affects the auditory nerve can lead to this type of hearing loss in PHACE syndrome. Sensorineural hearing loss is usually permanent.
- **Mixed hearing loss** is a combination of conductive and sensorineural hearing loss. Although this has been seen in PHACE syndrome, it is thought to be caused by factors other than the PHACE syndrome itself (i.e. coincidence).

### **How are hearing abnormalities diagnosed and treated?**

Children with PHACE syndrome will generally pass their initial newborn hearing screen, but may develop problems during the first year of life. Suspicions of hearing loss should be brought to the attention of the primary care physician. A referral to an otolaryngologist (ear-nose-throat doctor) or **audiologist** (hearing specialist) may be needed. If a child has hemangiomas on or around the ear and has been diagnosed with PHACE syndrome, a hearing test should be repeated during the first year of life.

If hearing loss is determined to be attributed to an intracranial hemangioma in the child, treatment to minimize the growth of the hemangioma can be started. Assistive devices are also available to improve hearing.

## Intracranial Hemangiomas

### **What is an intracranial hemangioma?**

An intracranial hemangioma is a hemangioma that is inside the head, within the skull. As patients with PHACE syndrome are screened with MRI and MRA, intracranial hemangiomas can be identified. These lesions are usually found near areas of the skull called the *internal auditory canal* (a channel containing nerves that connect the ear to the brain) or the **cerebellopontine angle** (space in the base of the brain between the cerebellum and the pons). Intracranial hemangiomas are usually located on the same side as the skin hemangioma.

### **What symptoms are seen with intracranial hemangiomas?**

Remarkably, most infants with a hemangioma in the head have no symptoms and no problems with movement, coordination, language, or sight. Further research needs to be done to determine if there are subtle effects that we may not yet know about. Hemangiomas located in the internal ear canal may cause hearing loss.

**How common are intracranial hemangiomas in PHACE syndrome?**

One study found 12% of patients with PHACE syndrome have intracranial hemangiomas. More intracranial hemangiomas are being identified in patients with PHACE syndrome now that MRI and MRA testing is becoming more common.

**How are intracranial hemangiomas diagnosed and treated?**

Intracranial hemangiomas are diagnosed through MRI and MRA of the brain. Children with a hemangioma in the internal auditory canal or signs of hearing loss should be evaluated for hearing loss.

Since most intracranial hemangiomas have no symptoms, they are often treated with observation alone. Patients may be given treatment to decrease the size of the hemangiomas if they are causing symptoms. In some cases, patients receiving treatment to manage their skin hemangioma will find that the intracranial hemangiomas usually decrease in size as well.

# Glossary

**Aneurysm:** a balloon-like widening on a part of a blood vessel

**Aorta:** the main artery which carries blood rich in oxygen from the heart to most other arteries in the body

**Aortic arch:** the part of the aorta which turns downward, giving the aorta its “candy cane” shape

**Audiologist:** a doctor who is a hearing specialist

**Basilar artery:** artery in the brain that supplies the pons, cerebellum and inner ear with blood

**Cerebellopontine angle:** a space in the brain between the base of the cerebellum and the pons

**Cerebrum:** the largest part of the human brain, filling most of the skull and consisting of two hemispheres divided by a deep groove. It is the center of thought, learning, memory, language and emotions

**Cerebrovascular abnormality:** an abnormal blood vessel that carries blood to the brain, located in the head or neck

**Cervix:** the technical name for neck

**Circle of Willis:** a circular group of arteries that provides a connection between blood flowing through the back and front of the brain

**Coarctation of the aorta:** narrowing of the aorta

**Common carotid artery:** an artery that supplies the head and neck with oxygenated blood. It divides in the neck to form the internal and external carotid arteries

**Computed tomography angiogram:** combines the use of x-rays and computerized analysis to show pictures of arteries throughout the body

**Conductive hearing loss:** occurs when there is a problem getting sound waves through the structures of the ear

**Dandy-Walker complex:** is diagnosed when several abnormalities of brain development are present together. These abnormalities are: enlarged posterior fossa, enlarged fourth ventricle, absence of the part of the brain located between the two hemispheres

**Deep hemangioma:** a type of birthmark made up of blood vessel cells which is located under the skin in the fatty tissue

**Dysgenesis/hypoplasia/atrophy:** underdevelopment or incomplete development of a tissue or organ

**Echocardiogram:** often referred to as an ECHO, is an ultrasound of the heart. It can be used to image the heart and assess blood velocity and cardiac function

**Electroencephalogram:** also called EEG, is the recording of electrical activity produced by the firing of neurons in the brain

**Endocrine system:** a system of glands which produce chemicals called hormones used to regulate the body

**Epilepsy:** a common chronic neurological disorder characterized by seizures

**External carotid artery:** the branch of the carotid artery that supplies blood to the face, tongue, and external parts of the head

**Hemiparesis:** weakness or loss of muscle function on one side of the body due to nerve damage

**Hypopituitarism:** decreased production of some of the hormones made by the pituitary gland

**Hypothyroidism:** deficiency of thyroid hormones

**Hypotonia:** a state of low muscle tone often involving reduced muscle strength

**Infantile hemangioma:** a common type of birthmark made of blood vessels which is usually not present at birth, and goes through a growth, rest, and shrinking phase

**Innominate artery/brachiocephalic artery:** the first branch of the aortic arch which divides into the right common carotid and right subclavian arteries. It supplies blood to the right arm, head and neck

**Internal carotid artery:** artery that arises from the common carotid artery in the neck and branches in the brain into the anterior and middle cerebral arteries.

**Magnetic resonance angiogram:** (MRA) a noninvasive technique used to evaluate the arteries of the neck and brain

**Magnetic resonance imaging:** (MRI) a noninvasive technique use to visualize detailed internal structures

**Microphthalmia:** developmental defect where the eye (or eyes) are smaller than normal

**Mixed hearing loss:** hearing loss due to both conductive and sensorineural problems (see those entries)

**Mixed hemangioma:** a hemangioma that has both deep and superficial components (see those entries)

**Morning glory disc:** an abnormality of the eye and its blood vessels that resembles the morning glory flower

**Neurologist:** a doctor who specializes in the nervous system

**Opisthotonus:** a condition in which the body spasms so the head and heels are arched backwards in extreme hyperextension and stiffness

**Ophthalmologist:** a doctor who specializes in the eyes

**Optic nerve hypoplasia:** a condition where the optic nerve is underdeveloped resulting in a smaller than normal optic nerve

**Otolaryngologist:** an ear, nose, throat specialist

**Patent foramen ovale:** A heart defect where the opening between the left and right atria which allows blood to bypass the lungs in utero does not close shortly after birth as it should

**Persistent fetal vasculature:** a condition where blood vessels in the retina that should disappear as the fetus develops inside the womb do not disappear

**PHACE Syndrome:** a condition in which a set of defects are present, mainly involving the Posterior fossa, Hemangiomas, Arteries, Cardiac (heart), and Eyes. Diagnostic criteria need to be met to make the determination of PHACE Syndrome

**Posterior fossa:** the space inside the skull which contains the brainstem and cerebellum

**Segmental hemangioma:** a type of birthmark made of blood vessel cells located across a large area of skin

**Seizure:** an abnormal burst of electrical signals in the brain which temporarily interrupts the brain's normal function

**Sensorineural hearing loss:** occurs when there is damage to the inner ear (cochlea), or to the nerve pathways from the inner ear to the brain

**Sternal cleft:** a groove or split in the sternum

**Sternal papule:** a raised bump on the skin overlying the sternum

**Sternal pit:** a small indentation or dimple in the skin overlying the sternum

**Sternum:** the bone in the front middle of the chest wall that joins the two sides of the rib cage

**Stridor:** a “barking cough” that is caused by an obstruction in the windpipe or larynx. In PHACE it may be due to a subglottic or airway hemangioma

**Stroke:** loss of brain function due to disturbance in blood supply to the brain

**Subclavian artery:** artery that branches from the arch of the aorta in the chest to supply blood to the arm

**Subglottic hemangioma:** a type of birthmark made of blood vessel cells located in the area directly below where the vocal cords are in the airway

**Superficial hemangioma:** a type of birthmark made of blood vessel cells located only on the surface of the skin

**Supraumbilical raphe:** a scar-like line that extends upward from the umbilicus (belly button)

**Ulceration:** when a patch of tissue breaks down and causes a sore

**Vascular ring:** abnormally formed blood vessels that make a ring around the trachea

**Ventricular septal defect:** opening in the ventricular septum that allows abnormal blood flow between the left and right ventricle of the heart

**Vertebral artery:** artery which branches from the subclavian artery and supplies blood to the back parts of the brain via the Circle of Willis