3. Neurology / Strokes

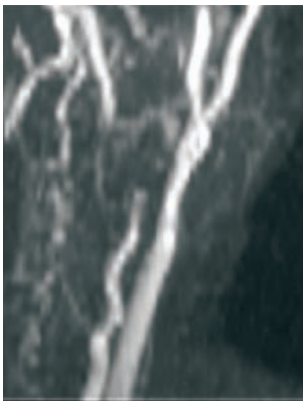
Strokes and cerebrovascular disease are one of the leading causes of morbidity and mortality in children with Progeria. The earliest published incidence of stroke is at the age of 4 years. In one case, seizures were the presenting cerebrovascular event. Importantly, stroke may occur while the child exhibits a normal ECG. As we continue to learn more about the types of neurological changes that occur in Progeria over time, we hope to positively influence clinical care of children with Progeria in the future.

Good hydration is very important in Progeria to help keep demands on the heart and blood vessels low.

Strokes and Transient Ischemic Attacks (TIAs)

In an effort to provide some clues into the increased susceptibility to developing strokes, a series of children with Progeria have been studied to evaluate the types of changes that occur in the blood vessels of the head and neck with increasing age. Although there are a number of changes that are being newly characterized, it is clear that there are some similarities among the children as a group. The most frequent of these is narrowing of the largest of the blood vessels in a region where blood flow from the neck transitions into the largest of the blood vessels in the portion that enters the skull at the base of the brain. Blood flow is blocked by narrowing or constriction of the blood vessels and, potentially, by blood clots.

Gradually the blood flow to the brain is slowed, which increases the likelihood of blood clot formation and can lead to strokes and TIAs. The blood vessels, in an attempt to compensate for the blockage, form collateral vessels, or



MRI of a 5-year-old showing complete blood flow blockage in the carotid artery of the neck

"side roads" to help with blood flow and to try to supply oxygen to the areas of the brain that were once served by the narrowed arteries. However, these new blood vessels are smaller and more fragile than normal blood vessels. In addition, these newer blood vessels are susceptible to shifts in blood pressure and hydration.

In children with Progeria, the first symptom is often stroke or recurrent ischemic attacks (TIAs, also called "mini-strokes", frequently accompanied by headaches, muscular weakness or paralysis affecting one side of the body, and/or seizures). Based on our experience, by the time the children present with neurologic symptoms from a stroke, there is often evidence of prior so-called "silent" strokes that have occurred in the past. Silent strokes are those that occur in brain regions that may not produce such dramatic symptoms, but over time may accumulate and cause more permanent symptoms. If a stroke with new clinical symptoms occurs, then management of blood pressure is imperative. In the case of a larger stroke, monitoring in an ICU is often indicated until the child's condition is stabilized. Medication treatments such as anticoagulation are often considered at that time.

Aspirin for stroke prevention

Drugs such as antiplatelet agents (like aspirin) are often given to prevent clot formation and to prevent future strokes from occurring. The reasoning behind using these types of medications is to prevent future strokes, especially in the areas where there is some narrowing of the blood vessels or partial blockage. Some doctors believe that all patients with this type of narrowing should be on a medication permanently as a preventative step. The decision to start aspirin and/or to add another type of medication to the aspirin should always be made by speaking to the medical team and/or consultation with a neurologist to guide appropriate care. Safety of many of these medications and guidelines for use are not well-established in pediatric patients and, therefore, careful evaluation is needed.

Headaches

Headaches are frequently observed in children with Progeria. This is likely at least in part to some of the changes in the blood vessels that are observed. Headaches can be single or recurrent in nature, and localized to one or more areas of the head and face. The exact causes of headaches are not completely understood. It is thought that many are the result of tight muscles and dilated, or expanded, blood vessels in the head.

To stop the headaches from occurring, treatment may include rest in a quiet, dark environment, avoidance of some known triggers such as certain foods and beverages, lack of sleep, and fasting. The most common food and beverage triggers are chocolate, cheese, nuts, shellfish, Chinese food (commonly containing mono sodium glutamate (MSG)), sugar, caffeine, and alcohol.

Medication treatments may be necessary to prevent and/or treat acute headaches if they occur frequently.

It's important to keep children well hydrated, especially during long trips.

Seizures

Seizures are brief, temporary disturbances within the electrical system of the brain. The most easily recognized seizure involves shaking movements of the body and a period of decreased awareness. Other, less obvious forms of seizures may affect a person's awareness, muscle control, or sensory perception.

Often, family members who witness a seizure will be asked to record details like the time of day that a seizure occurs, how long it lasts, what parts of the body are affected, and what the mental awareness is immediately before and after. This information can be quite helpful to determine the type of seizure present.

Doctors may recommend an electroencephalogram (EEG), which is a test where tiny electrode wires are attached to the head in order to record brain waves. An EEG can sometimes show changes in the electrical activity of the brain. A normal EEG does not exclude the diagnosis of seizure and patients may need additional monitoring as part of the evaluation. If the EEG is abnormal, the results can be used to determine if medications are necessary to prevent future seizures and, if so, may guide the choice of medication.

> What to do in the event of a seizure

Even if you feel frightened, it is important to stay calm and to stay with your child until the seizure stops. Notice when it starts and stops and what body parts are involved. If your child is sitting or standing, gently ease them to the floor and keep the head from falling backwards. Place your child on their side. It is important not to try to open the mouth or place anything between the teeth. Do not try to stop the movements or "shake" your child

Strokes can occur, even in the absence of known cardiac problems. Childhood stroke symptoms are similar to those of adult stroke. In particular, watch for speech difficulties, eye movement problems, or weakness/numbness in one region of the body.

out of it. After the seizure, your child may have lost control of bowel or bladder function. And he/she may be more tired or experience headache or soreness. Contact a doctor if at any time the seizure is prolonged (more than 5 minutes), if there is change in the skin color, and/or if the child has trouble breathing. It is common for children to be sleepy after a seizure; contact a doctor if the seizure is a new event for the child, if he/she cannot be fully awakened after 10-15 minutes, or if there are any additional concerns.

Imaging recommendations

It is recommended that children with Progeria undergo neuro-imaging studies to track disease progress and the presence of abnormalities such as silent strokes, new vessel formation in the brain, or vessel narrowing. This is best performed with a magnetic resonance imaging study (MRI) of the brain to screen for prior strokes. If possible, a magnetic resonance angiography study of the head and neck (MRA) should be done at the same time.

Sedation

Many young children will require sedation in order to get imaging studies of the brain or the body. Children with Progeria who are known to have cardiovascular or blood pressure abnormalities will require special attention when undergoing sedation or anesthesia. An evaluation by a qualified provider, such as an anesthesiologist or intensivist, is recommended prior to any planned sedation to discuss fluid and blood pressure management plans. See *Airway Management & Anesthesia*, section 5, for additional recommendations.

Special circumstances: Travel, hydration

Sudden onset of neurologic symptoms are often brought on by activities that involve over-breathing (hyperventilation), reduction in blood pressure, or dehydration. For these reasons, it is very important that children remain very well hydrated at all times. This is particularly crucial during times of illness and/or travel. Children who plan to travel should increase their hydration and fluid intake in the 24-48 hours prior to the start of the trip. As a rough estimate, minimum fluid requirements are about one liter daily, with a goal closer to 1.5 liters.