What are complex lymphatic anomalies (CLAs)?

CLA’s are a group of rare diseases that are characterized by abnormal growth of lymphatic vessels that may involve multiple organ systems, including lung, spleen, soft tissue and bones.

CLAs include:
- Gorham Stout Disease (GSD),
- Generalized Lymphatic Anomaly (GLA),
- Kaposiform Lymphangiomatosis (KLA) and
- Central Conducting Lymphatic Anomaly (CCLA).

CLA diseases have both common and unique features. In addition, individual diseases affect patients differently, and even patients with the same diagnosis may have different symptoms based on the location of the body that is involved.

What is the lymphatic system?

The lymphatic system is a network of tubes or vessels that drain lymph fluid from all over the body and return or deposit that fluid back into major veins in the chest.

Peripheral lymphatic vessels, in the extremities, are small and become larger as they move closer to the heart. Lymphatic vessels have specialized cells (lymphatic endothelial cells) and valves to keep the lymph moving toward the heart.

The main purpose or role of the lymphatic system is
- Maintain fluid levels in your body
- Absorb fats from the digestive tract
- Help fight infections
Lymphatic malformations are caused by abnormal growth of lymphatic vessels.

Important parts that make up the lymphatic system are:

- **Lymph**: clear fluid containing white blood cells that helps clear toxins and waste
- **Lymphatic vessels**: small tubes (vessels) that carry lymph throughout the body
- **Lymphatic endothelial cells**: specialized cells that line the lymphatic vessels to maintain structure, and valves to keep the lymph moving in one direction

A helpful video, on YouTube, describes the lymphatic system.
How are Genetics Involved with CLAs?

It is suspected that a majority of CLAs are caused by changes in genes called pathogenic variants (previously called mutations). However, not all patients are able to have a cause identified. These pathogenic gene variants can be somatic (mosaic) or germline.

**Acquired somatic variant or mutation:**
A change in DNA that occurs after conception - fertilization of the egg by sperm. Acquired pathogenic somatic variants can occur in any of the cells of the body except the germ cells (sperm and egg) and therefore are not passed on to children.

**Germline (or inherited) variant or mutation:**
A gene change in a body’s reproductive cell (egg or sperm) that becomes incorporated into the DNA of every cell in the body of the offspring. Germline pathogenic variants are passed on from parents to offspring.
Which disorders are considered CLAs?

**Generalized Lymphatic Anomaly (GLA)**

Formerly known as Lymphangiomatosis, GLA is characterized by lymphatic malformations involving soft tissues, bones, and organs such as the spleen with disease present in more than one location in the body.

GLA may present at birth but is more frequently identified in childhood or young adulthood. GLA can cause abnormal collection of fluid around the heart, lungs, or in the abdomen (pericardial, pleural, or peritoneal effusions, respectively). It can also cause loss of lymph fluid through the intestines (protein losing enteropathy), and low numbers of infection fighting cells.

Bone diseases are commonly seen, involving multiple bones of the axial (head and trunk) and appendicular (limbs) skeleton. The ribs are the most common site of involvement in GLA, followed by the spine. Bone involvement in GLA does not typically involve the outer hard layer of the bone (cortical bone) and rarely results in progressive bone disappearance. Fractures resulting from disease are uncommon.

Somatic pathogenic variants in the *PIK3CA* gene are thought to cause GLA.
Gorham Stout Disease (GSD)

Also called vanishing bone disease, GSD is characterized by progressive loss of the hard outer surface (cortex) of the bone. GSD can progress rapidly but can also spontaneously stabilize. It typically extends beyond the original site of disease, involving nearby bones, and is much more common in the head, neck, back and chest (axial skeleton).

Symptoms caused by GSD vary depending on the extent of the loss of outer hard layer of the bone (cortical bone) and its location in the body. Fractures resulting from disease (pathologic fractures), buildup of fluid around the heart and lungs (pericardial and pleural effusions) secondary to rib involvement, leaks of cerebral spinal fluid (CSF) resulting from skull-based damage, and neurologic symptoms including paralysis have all been reported.

Somatic pathogenic variants in the KRAS gene are thought to cause GSD.
**Kaposiform Lymphangiomatosis (KLA)**

KLA is a complex lymphatic anomaly with features of both uncontrolled cell growth (neoplasia) and malformation. KLA is considered an aggressive subtype of GLA and has characteristics that overlap with both GLA and CCLA. Unique features of KLA include the presence of spindle cells, rapid and progressive growth, and significant bleeding (hemorrhage).

In addition, chest involvement is much more common in KLA. Markers to help diagnose KLA include elevated blood levels of angiopoietin 2 (Ang2), a protein involved in endothelial cell growth.

Somatic pathogenic variants in either the *NRAS*, *CBL*, or *HRAS* genes are thought to cause KLA.

**Central Conducting Lymphatic Anomaly (CCLA)**

CCLA is characterized by dilated and dysfunctional lymphatic vessels in the torso leading to the backflow of lymphatic fluid into tissues. The dysfunction in part results from abnormal formation of lymphatic valves in the large lymphatic vessels.

Patients often present with lymphatic fluid around the lungs (chylous effusions), excess abdominal fluid (ascites), and loss of lymph fluid through the intestines (protein losing enteropathy) as well as swelling in the legs and feet.

Both germline pathogenic variants, in EPHB4 and MDFIC and somatic pathogenic variants in several different genes, are thought to cause CCLA.
The following chart outlines each CLA disease along with its old terminology, distinguishing features, and genetic correlation.

<table>
<thead>
<tr>
<th></th>
<th>GLA</th>
<th>GSD</th>
<th>KLA</th>
<th>CCLA</th>
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<tbody>
<tr>
<td><strong>Previous terminology</strong></td>
<td>Lymphangiomatosis</td>
<td>Vanishing bone disease</td>
<td>Lymphangiomatosis</td>
<td>Lymphangiectasia Channel type Lymphatic anomaly</td>
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<tr>
<td></td>
<td>Diffuse Lymphatic malformation</td>
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<tr>
<td><strong>Distinguishing features</strong></td>
<td>Disease affecting multiple parts of the body</td>
<td>Progressive bone loss</td>
<td>Spindle shaped lymphatic endothelial cells, low platelets, bleeding, high ang2</td>
<td>Abnormal structure and function of central lymphatic vessels</td>
</tr>
<tr>
<td><strong>Genetics, pathogenic gene variants</strong></td>
<td>Somatic: PIK3CA</td>
<td>Somatic: KRAS</td>
<td>Somatic: NRAS, CBL, HRAS</td>
<td>Somatic: ARAF, BRAF, KRAS</td>
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<tr>
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<td></td>
<td>Germline: PTPN11, RAF1, RIT1, SOS1, HRAS, BRAF, FOXC2, PIEZO1, GBA, GBE, Trisomy 21, 22q11.2 deletion</td>
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</table>
What are the symptoms of CLAs?

While symptoms vary between conditions and individuals, the following as a list of symptoms most commonly reported by CLA patients. These symptoms can present at the onset of diagnosis or throughout the progression of the disease.

- Coughing, wheezing, shortness of breath
- Pain surrounding affected areas
- Swelling surrounding affected areas
- Bone fractures (spontaneous or after minor trauma)
- Recurring infection or respiratory disease
- Abdominal or pelvic pain
- Skin lesions
- Internal bleeding

Symptoms vary based on the area of the body that is affected and can lead to unique and specific difficulties that greatly impact quality of life. Examples include mobility issues, malformation of bones, and neurological issues, which can become permanent and lead to lifelong disabilities.

How is it diagnosed?

Unfortunately diagnosing CLAs is not typically a straightforward process, with some patients taking many years to reach a diagnosis. Part of this is attributed to how rare these diseases are, but also overlap can be seen with other diseases and it can be especially difficult to determine which rare CLA a patient has.

Providers may recommend one or more of the following tests to aid in a diagnosis and monitoring:

- Biopsy
- Bone scan
- Bronchoscopy
- CT scan
- MRI
- Lymphangiogram
- Skeletal survey
- Ultrasound
- X-ray
- Blood tests
- Genetic tests
Imaging

MRI and/or CT imaging of affected areas is recommended as the first screening imaging for suspected CLAs. Skeletal survey or radiographs recommended as second imaging technique and for long-term monitoring. Dynamic contrast-enhanced magnetic resonance lymphangiogram (DCMRL) may be needed to image the central lymphatics.

Laboratory Evaluation

Laboratory evaluation includes:
- complete blood count (CBC), complete metabolic panel (CMP), coagulation studies, and
- immune testing may be required.

Genetic Testing

Genetic testing of involved tissue is needed to help identify potential causative pathogenic gene variants and guide targeted therapy. It’s important to keep in mind that
- affected tissue must be tested due to the nature of somatic variants (not present in all cells), and
- while affected tissue must be used for genetic testing, the number of cells that may carry the pathogenic variant is low, which can make it difficult to detect causal variants. Increasing the number of samples may increase the likelihood of positive genetic testing, and
- germline testing should be considered in all patients with CCLA and patients where CLAs are thought to occur as part of a syndrome.
What is the treatment for CLAs?

There is no standard approach for treatment for CLAs. Treatment is often aimed at reducing and easing symptoms. A multidisciplinary, team approach to care and treatment is highly recommended and often necessary.

Medications that have been commonly used to treat CLAs include:
- Sirolimus
- Alpelisib
- Interferon-alfa 2a or 2b
- Bisphosphonates

CLA patients receiving treatment with sirolimus may require prophylactic antibiotics to minimize serious infection (pneumocystis pneumonia).

Other treatments, that may be beneficial, include sclerotherapy or embolization, surgery, and lymphovenous anastomosis (LVA).

Nutrition

- Patients with chylous (lymph fluid with fat) effusions may be prescribed a low-fat diet.
- Patients treated with Sirolimus or Alpelesib may be prescribed a low carbohydrate diet as both medications tend to raise blood sugar.
Medical Centers
A list of global vascular centers that may be specialized in treatment of CLAs can be found on our website at lgdalliance.org.

Patient Support
For a list of patient resources, including our patient registry and support groups, please visit our website at lgdalliance.org

Contact
LGDA: www.lgdalliance.org or info@lgdalliance.org
LGDA_Europe: www.lgda.eu or info@lgda.eu for European inquiries