

Symptoms of ALD/AMN

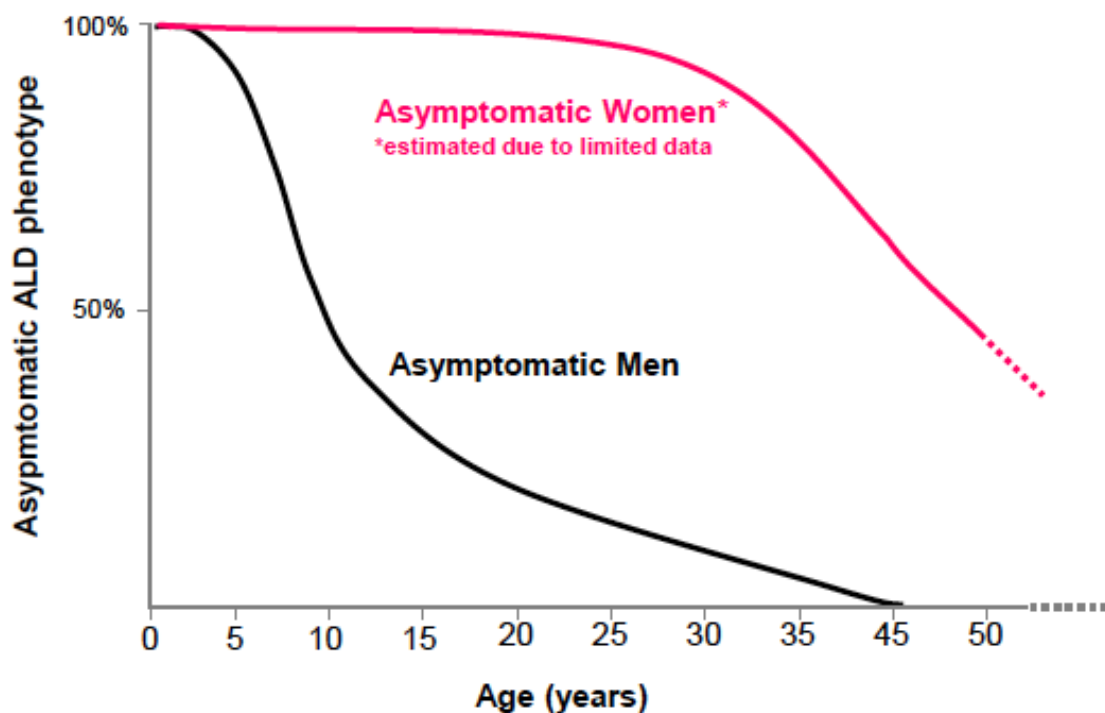
ALD symptoms can vary depending on age, gender, and the body tissues affected. The tissues that are most severely affected in ALD are myelin, blood, and the adrenal glands. Not all tissues are affected at the same time in all patients. In the world of genetic disorders, doctors group collections of symptoms into “phenotypes” based on the cells and tissues that are most severely affected by a gene abnormality. Individuals with the ALD gene may have different phenotypes. In ALD, the phenotypes are not mutually exclusive. In fact, it is common for individuals to have more than one phenotype at any given time.

There are 4 primary phenotypes that can occur in **MALES** with the ALD gene:

1. Asymptomatic (meaning no symptoms)
2. Adrenomyeloneuropathy (AMN)
3. Adrenal insufficiency
4. Cerebral demyelinating ALD (cerALD)

1. Asymptomatic phenotype

All individuals with the ALD gene are free of clinical symptoms for at least the first three years of life. And some may continue to have no symptoms. But as the diagram shows below, the percentage of asymptomatic men and women decreases with age.



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2. Adrenomyeloneuropathy (AMN) phenotype symptoms:

- Walking and balance problems

General leg weakness and stiffness progresses into walking difficulty and reduced balance. With the weakening of leg muscles, changes in gait, or how a person walks, becomes noticeable. The use of mobility devices, such as canes, walkers, and wheelchairs may become necessary.

- Pain, numbness, or tingling in the legs
- Mild to moderate weakness of the arms/hands
- Urinary problems or incontinence and bowel urgency or incontinence
- Sexual dysfunction, or the inability to obtain or maintain an erection

3. Adrenal insufficiency (Addison's disease) phenotype symptoms:

Adrenal insufficiency occurs as a result of permanent injury to the adrenal glands. Most men with ALD will eventually develop adrenal insufficiency over their lifespan. Women develop adrenal insufficiency much less commonly. Although it is easily treatable, adrenal insufficiency can be life-threatening if it is not recognized promptly. Symptoms are often non-specific and can include weakness/fatigue, nausea, abdominal pain, and low blood pressure. Darkening of the skin is also common.

Adrenal insufficiency is sometimes referred to as Addison's disease (based on the doctor, Thomas Addison MD, who first described it). There are many causes of adrenal insufficiency in the general population. ALD is the cause of approximately 33% of all cases of adrenal insufficiency. This means that not all patients diagnosed with adrenal insufficiency have ALD. Nonetheless, all patients with adrenal insufficiency should be tested for ALD (and vice versa).

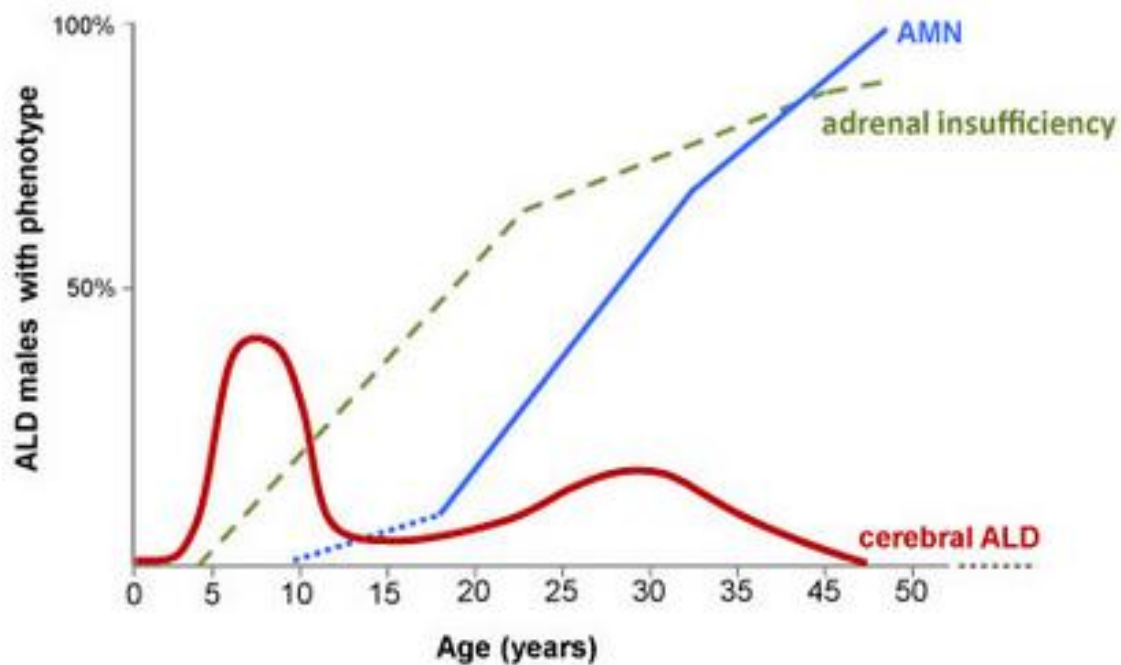
4. Cerebral demyelinating ALD (cerALD) symptoms:

Affected boys' symptoms may include "spacing out" in school: inattention, deterioration in handwriting skills, and decreased school performance; difficulty in understanding speech (though sound perception is normal); difficulty in reading and understanding written material; clumsiness; visual disturbances and occasionally double-vision; and aggressive or unexplained inappropriate behavior. In some boys, seizures may be the first symptom. Symptom severity varies from patient to patient and is not determined by phenotype. Even identical twins may have different experiences with symptom onset and severity. Other symptoms may include:

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- Behavioral problems
- Hyperactivity
- Eye pain/Childhood onset migraines
- Recurring viral infections
- Lethargy, tires easily, clumsiness
- Hypoglycemia
- Tanning or bronzing of the skin
- Adrenal insufficiency
- Attention deficit disorder (ADD)

The following diagram shows the likelihood of a male experiencing the symptoms described by phenotype above.



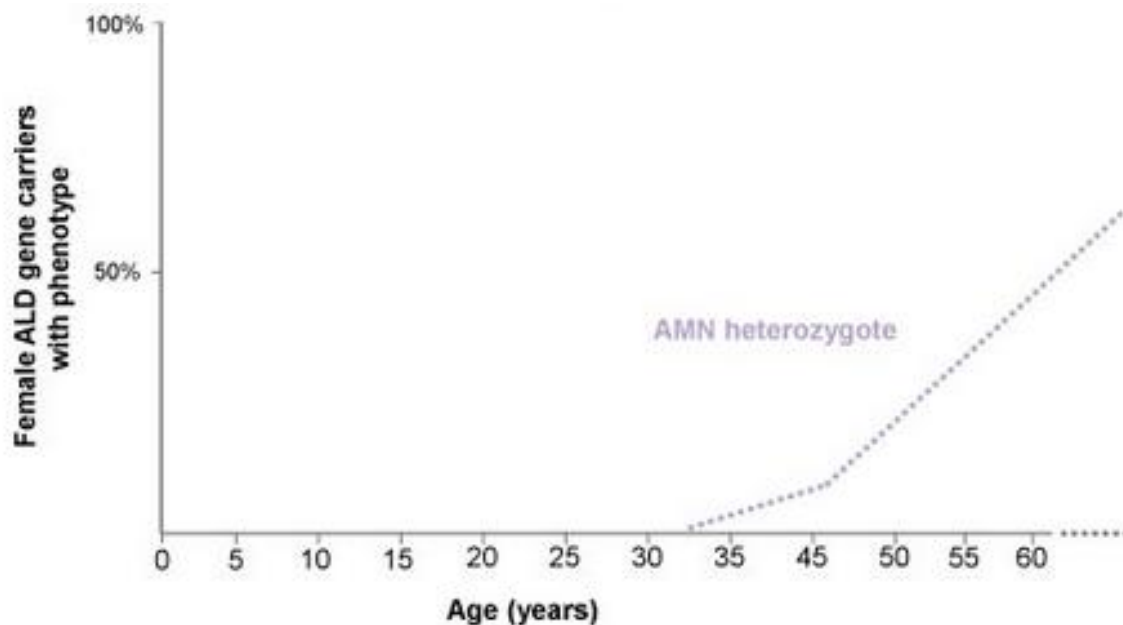
As mentioned above, a male who has symptoms associated with a particular phenotype may later develop other symptoms associated with other phenotypes. For example and as the diagram shows, men around 45 years' old will likely develop both adrenal insufficiency and AMN symptoms.

There are 2 primary phenotypes that can occur in **FEMALES** with the ALD genotype:

1. Asymptomatic
2. Adrenomyeloneuropathy (AMN)

Symptoms of ALD/AMN

Although cerALD and adrenal insufficiency are less common in women, they can occur and should be appropriately considered. Women experience similar AMN symptoms that men do. However, women generally have fewer symptoms that are less severe and develop later in life.



Although there is no known cure for ALD, there are available medications and therapies to treat many of ALD's symptoms. With increased understanding of the disease and the development of new therapies, we can look forward to many more in the future.