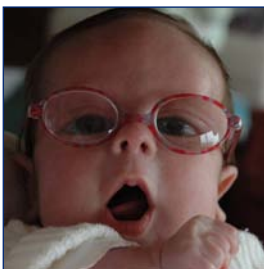


Lowe Syndrome Trust

A Guide for Professionals and Families



“Care today ... cure tomorrow”

LOWE SYNDROME TRUST

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FOREWARD

Oscar, our son, was born on the 26th November 1993 at 5.30am following eight years of hoping for a child. During those eight years I had two pregnancies. The first had resulted in a rare pregnancy called a Hydatiform Mole, which is a growth that forms inside the uterus at the beginning of a pregnancy instead of a foetus. Although in the majority of cases it isn't cancerous, in a few cases – around two or three in every hundred – the mole becomes a cancerous tumour called choriocarcinoma. Thankfully, following two years follow up with the Oncology department, I was given the all clear.

I miscarried at 12 weeks on the second pregnancy and was overjoyed but anxious when I discovered I was pregnant with Oscar.

Sadly the birth did not go well and following a traumatic delivery, we were told during the next few days that Oscar had a VSD (hole in the heart) and congenital cataracts which should be operated on within the next few weeks to save his vision.

The next five years were spent attending Great Ormond Street children's hospital for various tests to find out whether Oscar had a syndrome. We were told when he was age four that nothing could be found, but were devastated when Oscar was almost six, to find a new DNA test showed he had a rare incurable disease called Lowe Syndrome – with a life expectancy of perhaps seven.

Following the trauma of this news and within three months of discovering there was no UK support group or research into the disease, I set up the Lowe Syndrome Trust, Scientific Advisory Board, lobbied government and enlisted high profile celebrities to help raise awareness of the disease.

Some six years later, we have funded seven Lowe Syndrome research projects in the hope of better treatments and a cure. It has been a long, hard and emotional journey, but having a child with the disease takes over any thoughts one might have about giving up.

Oscar has progressed really well – although as I say to anybody who asks me – I never tempt fate as we know the dreadful symptoms of the disease and each day we live in fear of the unknown. Nobody can predict what will happen: will Oscar have seizures, epilepsy, rickets, arthritis, kidney deterioration, glaucoma? The list goes on. When we were first told he had a hole in his heart we were devastated, but now this is “just one of the list” of medical problems.

I cannot express the emotion of having a child with a rare incurable disease. Who can offer advice? How do you explain to people why he behaves in the way he does? People think we are awful parents who cannot control their child when he

lies on the floor screaming. How do we deal with it? It has been an incredible learning curve, not just the medical problems, but how life is different when you have a child with “problems”. We have learnt about the education system – or lack of it for special needs. The waiting lists for speech and language, physiotherapy and occupational therapies. We have learnt the bureaucracy of trying to get help with a child’s behaviour and the complicated issues associated with the State Tribunal System which you must use to get any kind of help for your child. You also learn about the expense of having a child with special needs, holiday clubs work out treble the cost as you have to pay for an assistant to be with him/her... but, that’s what we’re here for, the Trust has lots of advice and guidance to offer which we have included in this booklet.

Enough of the negativity.... Would I swap Oscar or wish he was born differently? Well actually, no. Of course we would swap the medical problems for a healthy Oscar. But I cannot explain the love that Oscar brings to us as a family. Lowe children are known to be loving, happy and cheeky little boys and that is so true. Oscar wakes up singing in the morning, loves life, and cannot bear to see anybody upset. Oscar has a unique personality and loves to make people laugh. He is now 12, although he looks and has the mental age of a 6/7 year old, and is only just understanding something about Lowe syndrome and now prompts me to tell people he has Lowe Syndrome Trust! Oscar adores swimming and is a lot better than most boys his age - he can play electronic games much better than most children – PS2/Gameboy and adores TV and videos.

We hope this book will help you understand more about the disease, but must stress that symptoms do vary from child to child.

The Trust is happy to discuss any queries you might have – details are as follows:

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1. Introduction

Lowe Syndrome (LS) is a rare genetic condition that causes physical and mental disability and medical problems. The condition almost always affects only boys and has wide ranging symptoms affecting the eyes, kidneys, brain, central nervous system and musculo-skeletal system – all the result of a single defective enzyme in the body. The boys suffer from medical problems throughout their lives and also have special educational needs. Sadly, their life expectancy is reduced due to the many complications of the disease.

Lowe syndrome was first recognized as a distinctive disease in 1952 by Drs. Lowe, Terrey, and MacLachlan at the Massachusetts General Hospital in Boston. They described three male children who had a similar set of problems that had not been previously associated with each other. Although they could not determine the cause of the disorder, they recognized a pattern to the symptoms and features and therefore described it as a “syndrome” - a set of symptoms which occur together.

The condition became known as “Lowe syndrome” after Dr. Charles Lowe, the senior member of the group that described it. Lowe syndrome is also known as the “oculo-cerebro-renal” syndrome of Lowe (OCRL), reflecting the three major organ systems involved in the disorder (eyes, brain, and kidney).

In subsequent years, doctors learned that Lowe syndrome is a genetic condition that affects only males. It is caused by a single defective gene on the X-chromosome, one of the two sex-determining chromosomes (see [IV. Genetics](#)). Normally, this gene produces a specific enzyme that is essential to inositol metabolism. Because the gene is defective in Lowe syndrome, the enzyme cannot be produced, causing the many and varied symptoms seen in affected children.

The Lowe Syndrome Trust was founded in June 2000 by Lorraine and Andrew Thomas following their five year old son’s diagnosis of Lowe Syndrome and the discovery that there was neither UK research into the disease nor specialist support for families. The aim of the Trust is to raise funding to support medical research in the hope of discovering better treatments and eventually a cure.

This booklet is part of the LST’s ongoing work to support families by ensuring that they are as well-informed as possible, to provide information to health professionals who may know very little about the disease, and to increase understanding of this condition for anybody who may encounter a child with Lowe Syndrome. It offers information about the medical effects of Lowe Syndrome and their treatments, the educational needs of children with Lowe Syndrome, the effects that living with Lowe Syndrome can have on a family as well as current research into the disease. It also provides useful contacts for parents and professionals dealing with a child with Lowe Syndrome. Well-

informed parents working together with caring and knowledgeable professionals can provide the best possible help and support for children and young people affected by Lowe Syndrome.

Some of the information in this booklet is quite technical and some of it may seem very daunting. Use it as a resource to dip into when you need to, discuss it with your medical team, friends and family, and feel free to contact the Trust if you want to discuss anything you read.

2. Lowe Syndrome – the low-down

What is Lowe syndrome?

Lowe syndrome (LS) is a rare genetic condition affecting males that causes physical and mental disabilities and medical problems. Also called the oculo-cerebro-renal syndrome of Lowe (OCRL), it was first described in 1952 by Dr. Charles Lowe and colleagues.

What causes Lowe syndrome?

Lowe syndrome is caused by a defective gene (the 'LS gene') that results in the deficiency of an enzyme called phosphatidylinositol 4,5-biphosphate 5 phosphatase. The enzyme is essential to normal metabolic processes that take place in a part of the cell called the Golgi apparatus. The enzyme deficiency leads to various developmental defects including cataracts and problems in the brain and kidneys. How the enzyme deficiency leads to these defects is not yet completely understood.

Why can't the missing enzyme just be replaced?

Scientists must first better understand the subtle imbalance caused by the biochemical defect. It is possible that overcorrection could be just as harmful as the original lack of the enzyme. Furthermore, there is currently no method available to target therapies to the areas of the cell where the LS enzyme is located. As the missing enzyme impacts tissue all over the body, it would be very difficult to target gene therapy.

How does someone 'get' Lowe Syndrome?

LS may occur either through inheritance of the LS gene or via a spontaneous mutation. If the former, the boys inherit the defective gene from their mother. In the latter case, LS is the result of an original mutation and the mother is not a carrier of the defective gene. This can be determined by testing. The LS gene is located on the X-chromosome, meaning that it is 'x-linked' and it affects only boys. Females who have the LS gene are known as 'carriers'; there is a chance they will pass the defective gene to their sons but they are not affected by the syndrome themselves.

Can LS be prevented?

In families in which a case of LS has occurred, female relatives can be tested to determine whether they carry the defective gene as they may be at risk of having an LS son. A 'slit-lamp eye examination' is currently used to determine whether a woman carries the LS gene; this may be used in conjunction with a DNA test for the specific mutation shown in the family. Various family planning options are available, including prenatal testing. Families should consult with a geneticist to learn more about their options at the earliest opportunity.

How is LS Diagnosed?

The characteristic cataracts and low muscle tone (hypotonia) are detectable at birth or shortly thereafter and offer an early indication of the disease. A DNA test can be carried out by a specialist laboratory in the UK. Depending on the type of mutation, a skin test may also be needed for a definitive diagnosis. In this instance, a skin sample is taken and sent for analysis at a laboratory in America. Physicians and families should contact the Lowe Syndrome Trust to find further information on these tests.

What are the common features of LS?

Cataracts in both eyes, found at birth or shortly after

Poor muscle tone (hypotonia) and delayed motor development.

Glaucoma (in about 50% of cases)

Mental retardation, ranging from borderline to severe (in a few cases intelligence may be normal)

Children tend to show symptoms of autistic spectrum disorder and have behavioural problems.

Seizures (in about half the cases)

Significant behaviour problems (in many, but not all, cases); children are often on the autistic spectrum.

Kidney involvement ("leaky" kidneys, or renal tubular acidosis)

Short stature

Cysts

Undescended testicles

Constipation

Dental problems

Life span may be shortened due to progressive kidney failure, although death may occur at earlier ages due to renal failure or other causes. Life expectancy may increase as knowledge increases and new treatments are developed.

How is LS treated?

There is no cure, but many of the symptoms can be treated effectively through medication, surgery, physical and occupational therapies, and special education.

What research is underway?

In 1992 the gene that causes LS was found. In 1995 researchers discovered that the gene defect causes an enzyme deficiency. Since the Trust was founded, several research teams have been funded in the UK to investigate the function of the gene and the biochemistry of LS. There is a great deal of research ongoing and the Lowe Syndrome Trust organises an International Symposium every two years to facilitate the sharing of research. Other areas of research in recent years include behaviour problems and clinical care. Information about current research can be found in this booklet or contact the LST for a current fact sheet.

What are boys with LS like?

Generally, they are affectionate and sociable, love music, and have a great sense of humour. However, they may also suffer from serious behavioural problems.

How many boys are there with LS?

Low syndrome is a rare disease. It has been identified in most cultures around the world and seems to have the same frequency in all populations although no one knows exactly how many individuals have Lowe syndrome. The precise mutation that causes the disease varies from family to family – over 65 different versions of the LS gene have been identified in the UK so far. The disease varies in its symptoms and severity. There are no official statistics on the prevalence of the condition and this is an area that the Lowe Syndrome Trust is working on.

2.1. Lowe Syndrome Timeline

Every child with Lowe Syndrome is different but this summary gives a quick overview of some of the main medical features and an indication of when they might appear. **It should be considered a rough guide and not necessarily a comprehensive one.**

Birth	Cataracts, hypotonia
0-teens	Corneal degradation (50%) – keloids
0-1 years	Fanconi syndrome (kidneys) becomes apparent (if not, kidneys should be tested 3 monthly so that it is detected in a timely fashion). Loss of deep tendon reflexes (e.g. knee jerk). Undescended testicles
3-4	Rickets may develop
0-10 years	Glaucoma may develop (50%) Febrile convulsions Nystagmus/strabismus
6 onwards	Bone fractures (as boys learn to walk)
10 onwards	Kidney failure may commence
Older children	Major motor/generalised convulsions
8-13 years	Likely to be a time of particular behavioural difficulties
Early teens - adulthood	Development of scoliosis (50%) Joint swelling and arthritis
Throughout life	Increasing risk of hernias

3. Medical Features

Low Syndrome is a very rare disease (1 case in every 500,000 of the population) that is more common in males than in females, because it is carried by the X (from mother to son) chromosome. To date, research into this inherited disorder has been very limited. This section describes the more common and well documented signs and symptoms of Low Syndrome. It is not meant to be comprehensive, because different children will show the signs or symptoms listed below to a greater or lesser and extent and their severity will also vary from one child to another. Great Ormond Street is the centre of clinical knowledge about Low Syndrome in the UK.

3.1. Diagnosis

A physician considers a diagnosis of Low syndrome when there are **cataracts** in both eyes at birth and **hypotonia** (floppy baby syndrome) especially if there is a family history of the condition.

Diagnosing Low syndrome early in infancy is not always simple and straightforward. Although the cataracts and low muscle tone (hypotonia) are detectable at birth or shortly thereafter, eye, kidney and nervous system manifestations may only develop later. As the disease is so rare, it may not always be recognised straight away.

Low Syndrome may be diagnosed by **DNA testing** a blood sample to look for the LS gene (see Genetics section). In some cases (depending on the type of mutation) this will not yield a sufficiently clear answer and a definitive diagnosis of Low syndrome can be made by testing for a specific enzyme in skin cells. In this procedure, a small **skin sample** is taken from the patient, usually by a local GP. The sample must be sent to a specialized biochemical laboratory for culture and analysis. The skin biopsy may need to be taken under sedation due to the behavioural problems of many Low children and for this reason is only used when necessary. For more information on testing, see the section on genetics.

3.2. Eyes

The ocular features of Low syndrome include congenital cataracts in both eyes (in 100% of cases), glaucoma (in 50% of cases), corneal degeneration, strabismus (crossed eyes), and nystagmus. The effectiveness of treatments for these conditions varies and any of these conditions may cause significant visual disability.

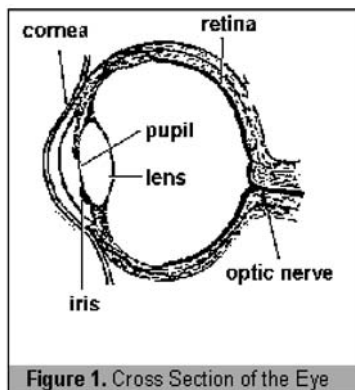


Figure 1. Cross Section of the Eye

3.2.1. Cataracts

In affected males cataracts are usually present at birth, although they may not be discovered until the child is several weeks old. A cataract is a painless ‘clouding’ of the lens of the eye. The lens is normally clear and transparent, like a camera lens and has much the same function. It focuses light onto the retina, which is at the back of the eye. The retina is like the camera film and records the image of what we see, which is then transmitted to the brain (where it is processed) by the optic nerve.

A cloudy lens reduces the amount of light that can reach the retina, so images are not seen clearly. It is important to remove a cataract as early as possible, preferably within the first few days or weeks of life, so that the baby can learn to see normally. If the cataract is not removed until later in life, the visual system may not learn to process images properly and the eye can be left blind. Early removal of cataracts facilitates proper development of the visual system.

Cataract Operations

The abnormal lens is removed surgically under a general anaesthetic. A small opening is made into the eye, typically at the edge of the zone where the clear cornea joins the white of the eye. Ultra-sound energy is used to break up the cloudy lens (cataract), which is then removed through a small tube. The capsule (in which the lens is contained) is usually also removed.

This operation improves the passage of light through the eye. However, as the lens has been removed, the eye cannot focus light onto the retina and strong glasses or contact lens must be used to compensate for this. For most children there is significant improvement in vision.

Artificial lenses

Surgical implantation of an artificial lens is not usually recommended for several reasons. These include: the small size of the eye of an infant and the inability to predict reliably the “adult size” of the eye in later in life; the possible complication of glaucoma (high pressure inside the eye – see below), which is common in Lowe syndrome; the risk of complications of further surgery; the uncertainty of long-term stability of an artificial lens in an infant and the possibility of problems with the cornea in Lowe syndrome. Some ophthalmologists (eye specialists) are now investigating the implantation of newer artificial lenses in children.

3.2.2. Glaucoma

Glaucoma develops in about half of boys affected with Lowe syndrome. Glaucoma is a disease in which the pressure inside the eye becomes high and can damage the retina and optic nerve, leading to loss of sight. The pressure can sometimes be so high that the eye bulges out - buphthalmos.

Treatment of infantile glaucoma is difficult. Medicinal eye drops may be tried first to try to lower the pressure, but they are rarely effective by themselves. If eye drops do not work, various surgical procedures may be tried. Laser treatment (diode laser) can be used to reduce the amount of fluid the eye makes. A new channel can be created to allow the fluid inside the eye to leave more easily and thereby to lower the pressure. Sometimes an artificial valve with a small tube is sutured into the front of the eye to control release of fluid and thus decrease the pressure. Unfortunately, in some cases glaucoma is so severe it cannot be controlled, ultimately causing the eye to become completely blind.

The risk of glaucoma is the major reason for routine examinations of the eyes during infancy and childhood. Although the risk of glaucoma lessens considerably after the first year, it may develop even after 10 years of age.; hence the need for regular check ups. Due to the complications of Lowe Syndrome, it may be necessary for these check-ups to occur under anaesthesia.

3.2.3. Corneal degeneration

The cornea is the clear “watch glass” cover on the front surface of the eye. By their teens about half of boys with Lowe syndrome develop what appears to be scar tissue, often called a keloid or fibroma over the cornea. The reason for this is not known, but like a cataract, it can impair vision and may need to be surgically removed. This is not always successful and may itself create more scarring. A cornea transplant may be an option if surgical removal does not work but post-operative care can be prohibitively complex for children with Lowe Syndrome.

3.2.4. Strabismus

Many children with Lowe syndrome develop squints (strabismus) or crossed eyes, a condition in which the eyes are not aligned and do not move together properly. In infants, this usually means that one eye is turned in. In infancy it can adversely affect the development of visual systems in the brain and impair eyesight. Treatment involves a complete assessment of the movements of the eyes and their muscles, eyesight and prescription of the right sort of glasses.

Treatment continues by patching one eye (usually the preferred or straight eye, in order to force improvement in the “lazy” eye with the poorer sight). As soon

as the child can follow a target equally well with each eye, surgery is performed on the muscles of the eyes to align them. If vision is equal, there is a good chance that the eyes will remain aligned after surgery. After surgery for strabismus the child should be followed carefully for any recurrence of the problem

3.2.5. Nystagmus

The term nystagmus refers to an uncontrollable and rhythmical movement of the eyes. While nystagmus by itself does not cause loss of vision, it is often caused by conditions related to poor vision. Occasionally it can be caused by changes in brain function. The genetic defect that causes Lowe syndrome can also affect the development of the retina in the eye (which is part of the brain). Unfortunately, there is no good permanent treatment for nystagmus, aside from taking all possible steps to develop and retain good vision from an early age, as described above.

3.2.6. Enucleation

Under very rare circumstances when an eye has become blind and painful, it may need to be removed to help ensure that the face develops normally. A “glass eye” can be fitted if wanted for cosmetic reasons.

3.3. Brain and central nervous system

The nervous system includes the brain, spinal cord, and nerves, and it governs the muscles. Lowe syndrome causes problems in most of these areas, including intellectual impairment, seizure disorders, behaviour problems, physical changes in the brain, and hypotonia or poor muscle tone.

3.3.1. General Learning Difficulties

The extent of learning difficulties in individuals with Lowe syndrome varies widely. Between 10-25% of individuals have an IQ at the lower end of the ‘average’ range, and another 25% have mild to moderate general learning difficulties. Others have severe learning difficulties. Although it is not possible to predict learning ability at birth, intelligence appears to be stable over the life span of most individuals.

3.3.2. Seizure disorders

Seizures occur in about half of all boys with Lowe syndrome. Younger children may have febrile convulsions (seizures caused by fever). These do not usually require medication unless they recur. In older boys, seizures are usually of a major-motor or generalized type. In many cases, these seizure disorders respond well to medication (anticonvulsants or antiepileptic drugs, also known as AEDS). Some individuals develop **refractory or 'resistant' epilepsy** or seizures that are difficult to control. The use of the newly-developed **vagus nerve stimulation** device, or "pacemaker for the brain," is under investigation for individuals with Lowe syndrome. This device consists of an implanted generator and a nerve stimulation electrode which transmits antiepileptic electric signals to the brain through the vagus nerve in the neck.

Individuals with seizure disorders will need an **EEG** (electroencephalogram) test to detect abnormal brain wave patterns and occasionally help to locate the place in the brain where the seizure(s) begin, and may assist in the diagnosis and treatment of the seizures.

3.3.3. Behaviour problems/Autistic Spectrum Disorder (ASD)

Although boys with Lowe syndrome are often happy, loving, and very sociable, many also have a characteristic pattern of behaviours that may interfere with everyday functioning. These include temper tantrums, stubbornness, unusual repetitive movements (especially of the hands), inability to concentrate or focus, and unusual obsessions or preoccupations. Some individuals may become violent and self-abusive. These behavioural patterns are thought to be a specific feature of Lowe syndrome. Some evidence suggests that for many individuals, the most difficult period for behaviour problems is between the ages of 8-13 years. In some cases, however, severe behaviour problems continue into adulthood. Behaviour modification techniques may be helpful for some. In some cases medication therapy may be effective. Some individuals have experienced improvement with the help of antidepressant and/or antipsychotic medications. Early intervention is key in managing behaviour. There are many different educational approaches for children with ASD and the most appropriate may vary from child to child. Advice may be sought from your LEA or from various autism charities (see contacts section).

3.3.4. Physical changes in the brain

Brain images generated by MRI (magnetic resonance imaging) may demonstrate abnormalities in the brain's **white matter**. These abnormalities are caused by tiny fluid filled cysts which develop during the first year of life. Whether this is a cause or effect of impaired brain function is unknown as yet. Brain atrophy, or shrinkage, has also been reported.

3.3.5. Hypotonia

Hypotonia, or poor muscle tone, is always present at, or soon after, birth. Hypotonia results in a “floppy” appearance and poor muscle strength. During infancy, hypotonia causes problems with head control and feeding (due to poor sucking). As the boys grow up, motor development is generally delayed in most areas. For instance, learning to **walk** is usually significantly delayed. About 25% of boys with Lowe syndrome develop the ability to walk alone between the ages of 3 and 6 years old. By the age of 6-13, 75% of boys with Lowe syndrome have developed the ability to walk.

Although the hypotonia improves slowly with age, most individuals do not reach normal muscle tone or strength, and related problems can occur as they grow older. Loose or hypermobile joints are also common due to the poor muscle and tendon strength. About half of all affected boys will develop scoliosis, or curvature of the spine, due to weakness in the back muscles. The greatest risk for developing scoliosis occurs during the early teenage through adult years. There is also an increased risk of developing hernias throughout life due to weak abdominal muscles. Eating problems may also result from poor muscle tone (see “Eating Difficulties” in General Health Concerns).

Hypotonia in Lowe syndrome is due primarily to nervous system dysfunction. Individuals have a slight blood elevation of a muscle enzyme called **creatinine kinase** (CK). Special **muscle tests**, such as EMGs (electromyography) or muscle biopsies, typically have normal or minimally abnormal results and are not needed to establish a diagnosis of Lowe syndrome. **Deep tendon reflexes** (such as the knee jerk) are usually absent by the first birthday. This may be due to nerve damage, which has occasionally been detected, but may also be due to nervous system dysfunction in the spinal cord. The absence of these reflexes causes no interference with normal function.

The most effective treatment for hypotonia is physiotherapy, begun early in infancy if possible.

3.4. Kidneys

Kidneys cleanse the blood and keep salt, water and acidity in balance. It takes anything that the body doesn’t need from the blood and filters it into urine, which leaves the body. This happens in two stages; firstly the blood is filtered by the ‘**glomeruli**’ (tiny filters) which hold back the blood cells and large molecules; secondly any small molecules that are needed are reabsorbed into the bloodstream by the **kidney tubules**. The unneeded parts are excreted in urine.

3.4.1. Renal Fanconi Syndrome

The primary kidney problem in Lowe syndrome is **Renal Fanconi Syndrome**. This is a deficiency in the reabsorption stage of the kidney process as the tubules are abnormal (see above). Substances that should be reabsorbed, such as bicarbonate, potassium, magnesium amino acids, organic acids, calcium, phosphate, glucose, and L-carnitine, are lost and the body becomes too acidic. Renal Fanconi syndrome can also be seen in certain other diseases and syndromes. In Lowe syndrome, the Fanconi syndrome may be mild and involve only a few substances or may be severe and involve large losses of many substances.

The symptoms of Fanconi syndrome include excessive urination, excessive thirst, dehydration, constipation, vomiting, elevated levels of glucose, phosphate, calcium, uric acid, amino acids and protein in the urine; elevated levels of chloride and decreased levels of phosphate and calcium in the blood and overly acidic blood. These lead to bone diseases and rickets over time.

The clinical signs of kidney abnormalities in Lowe syndrome are often not present at birth, but usually become apparent by one year of age. Doctors who are not aware of this delay may be reluctant to diagnose Lowe syndrome during the first year if the blood and urine tests of kidney function are normal. In a child suspected to have Lowe syndrome, **screening tests** (urine and blood tests) for kidney abnormalities should be done about every three months in the first year of life, then at least yearly thereafter until the Fanconi syndrome becomes apparent.

Treatment consists of reducing sodium chloride (table salt), giving antacids to reduce the acidity of the blood and giving potassium supplements. Most individuals respond to replacement therapy in which medication is given to replace the lost substances. The type of medication and dosage must be individualized for each patient by his doctor. Blood and urine testing is done at intervals to monitor the benefits of therapy and to determine the appropriate doses of replacement medication. In addition, because the kidneys are often not able to conserve water and concentrate urine normally, a larger than normal intake of fluids may be needed to prevent dehydration.

The kidney abnormality in Lowe syndrome may also cause **other abnormal laboratory findings**, including high cholesterol levels, particularly high-density-lipoprotein cholesterol. Generally, this is the result of the renal Fanconi syndrome. Other laboratory abnormalities that are common in Lowe syndrome include high levels of liver function enzymes SGOT and LDH. In most cases, these findings are not the result of liver problems, but rather the result of impaired muscle integrity. Generally, these lab findings are not a cause for concern.

3.4.2. Nephrocalcinosis

Nephrocalcinosis is a kidney disorder in which calcium and oxalate or phosphate are deposited in the kidney tubules and the areas in between them. This may result in impaired kidney function.

Excessive loss of calcium in the urine can be part of the Fanconi syndrome and can be associated with kidney stones and deposits of calcium in the kidney tissue - nephrolithiasis. Patients with Lowe syndrome appear more likely to develop these conditions than other children with diseases associated with Fanconi syndrome. Extra citrate in the urine can combine with calcium to help keep the calcium in solution and prevent nephrocalcinosis and stones. Vitamin D therapy for treatment of rickets (see [Rickets and Soft Bones](#)) should be carefully monitored in patients with Lowe syndrome to avoid worsening nephrocalcinosis. Calcium supplements should probably be avoided, unless the blood calcium is low.

When nephrocalcinosis or nephrolithiasis occur, they may also cause microscopic amounts of blood to appear in the urine. Nephrocalcinosis is best diagnosed by renal ultrasound and a plain abdominal X-ray. If a patient is suspected of having a kidney stone, a contrast X-ray study of the kidneys, like a CT scan (computed tomography) or intravenous pyelogram, may be needed to identify the exact position of any stones. A spot “urine calcium to creatinine ratio” or a 24-hour urine calcium measurement may be needed to determine the extent of calcium wasting and its subsequent response to any therapy. The use of thiazide diuretics may be useful in some patients with nephrocalcinosis or stones.

3.4.3. Kidney Failure.

Later in life, usually starting after the age of 10 years, the tiny filters of the kidney (the glomeruli) may start to fail. The exact cause of the filtration failure in Lowe syndrome is unknown. Kidney failure is diagnosed when waste products, like creatinine and urea nitrogen, begin to accumulate in the blood instead of being filtered out. This may begin to happen even before any physical symptoms occur. Creatinine and urea nitrogen are made every day by normal body metabolism and are good markers for kidney filtration. Creatinine is made by the muscles, so blood levels of creatinine may be lower than expected for a given degree of kidney failure if the muscle mass is decreased in Lowe syndrome. In that case, a 24-hour urine creatinine clearance gives a more accurate estimate of the kidney function than the blood creatinine alone. Symptoms of fatigue, decreased appetite, nausea, and vomiting may occur when kidney function is less than 20% of normal but are often non-specific.

Kidney failure usually progresses slowly and is not complete until age 30 or 40 years. Since few patients are older than 40, it is difficult to know what the late renal history of most patients will be and whether chronic dialysis or kidney transplant would be a good therapy for patients whose kidneys completely fail although some patients have been successfully treated with kidney transplantation.

3.5. Bones and joints

3.5.1. Rickets and soft bones

Many children with Lowe syndrome have a history of soft bones or rickets. This condition probably results from a combination of problems. As bones grow and form they need to “ossify” or become solid. Phosphate, calcium, vitamin D, other nutrients and hormones, and proper acid-base balance, are needed for proper ossification and bone remodelling with growth. Vitamin D is normally converted to its active metabolite, 1,25-dihydroxy vitamin D or calcitriol, in the kidney tubules. Since the kidney tubules are abnormal in Lowe syndrome, some patients may not make enough calcitriol to keep the bones strong and to enhance intestinal absorption of phosphate supplements. In addition, muscle tension on the bones due to exercise and movement is also thought to be necessary to keep the bones strong. When the muscles are weak (hypotonia), they do not perform this function well. **Low blood phosphate, acidosis (from renal Fanconi syndrome), hypotonia, and kidney problems in Lowe syndrome all place the boys at risk of developing soft bones, rickets (in the growing child) or osteomalacia (in the adult).** Problems associated with these conditions include fractures and scoliosis.

Rickets or osteomalacia can often be improved by giving vitamin D with oral preparations of neutral phosphate, as well as alkali salts like sodium and potassium bicarbonate to help correct the electrolyte losses due to the Fanconi syndrome. A side effect of **oral phosphate** is loose stools, so the dosage must be started low and carefully monitored. Occasionally, vitamin D metabolite preparations, such as calcitriol or dihydrotachysterol, are needed. Therapy with these medications should be carefully monitored to prevent the complications of kidney stones or calcium deposits in the kidney tissue (see “Nephrocalcinosis” in Kidneys). Since patients with Lowe syndrome may be predisposed to developing kidney calcifications even without vitamin D metabolite therapy, the kidneys should be checked for this condition by ultrasound or X-ray before starting, and at intervals during, any therapy with vitamin D metabolites. Plain vitamin D (parent compound) may not be effective as therapy because it may not be converted by the kidneys to the active metabolite.

All medications and dosages must be individualized for each child by his doctor. Blood and urine tests and X-rays are usually ordered periodically. **Blood tests**

may be done to measure calcium, phosphorus, bicarbonate, alkaline phosphatase, vitamin D metabolites, and parathyroid hormone:

Alkaline phosphatase is an enzyme made in bone. When the bone is actively breaking down as in rickets, or when the bone is actively growing and forming new bone as during healing of rickets, the blood level of alkaline phosphatase will be elevated.

The **metabolites of vitamin D** that are measured are 25-hydroxy vitamin D, which is made in the liver, and 1,25-dihydroxy vitamin D or calcitriol, which is made in the kidney. The 25-hydroxy vitamin D level indicates whether the dietary intake of vitamin D is adequate, while the calcitriol level indicates whether the kidney is making adequate amounts of this substance for bone growth and prevention of rickets.

Parathyroid hormone is a hormone made in glands in the neck near the thyroid. Parathyroid hormone regulates calcium levels in the body and may be elevated when a patient has rickets or is receiving too much phosphorus supplementation.

Urine tests may be done to measure phosphorus, calcium, albumin, creatinine, and pH and will indicate the severity of the urinary losses of calcium, phosphorus, albumin, and bicarbonate.

Changes for all medications should be made only by the doctor since medical problems may develop if the medication doses are too high or too low.

3.5.2. Fractures

About half of boys experience bone fractures, which often involve the upper leg when they are learning to walk at about 6 years of age. A third have more than one fracture, usually involving the arms and/or legs. Some fractures can probably be prevented if careful attention is paid to early diagnosis and treatment of hypophosphataemia (low blood phosphate levels), acidosis, and rickets or osteomalacia.

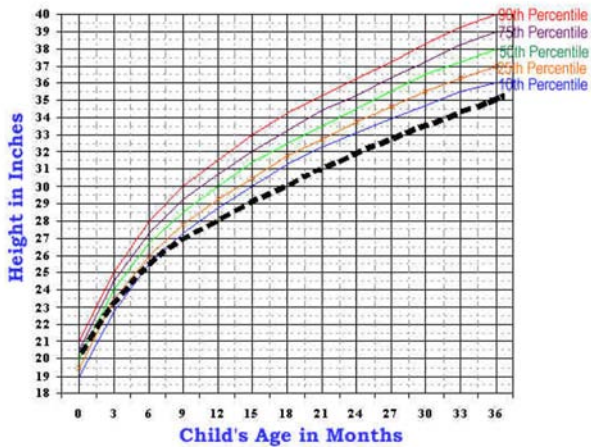
3.5.3 Scoliosis

About half of boys develop scoliosis, or curvature of the spine, by adolescence or adulthood. The severity of this condition varies from mild to severe. In severe cases, scoliosis can adversely affect mobility and cause back pain and diminished lung capacity. In some cases, this condition is treated effectively through the use of a brace or cast or surgery.

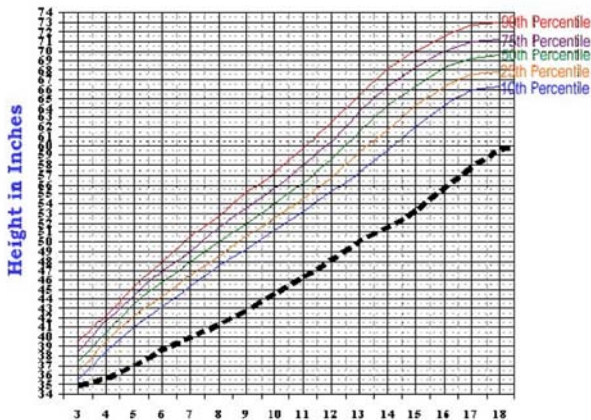
3.5.4. Short stature

Boys with Lowe syndrome are generally of normal length at birth but by one year of age, most have fallen well below the normal range of height (see Figures 2 and 3 below). Growth continues, but at a slower rate than normal. The average adult height is about 5 feet, 1 inch or 155 cm. The underlying cause of the short stature is unknown. Studies are being done to determine the effectiveness and safety of human growth hormone therapy. Reportedly, several children with Lowe syndrome have been successfully treated with human growth hormone. However, the effectiveness and the benefits of the supplementation must be balanced against the significant expense of the therapy and the potential social and psychological factors.

Boys Height Growth Chart (inches)
Ages 0-36 Months



Boys Height Growth Chart (inches)
Ages 3 - 18 Years



3.5.5. Joint swelling and arthritis

Other orthopaedic problems associated with Lowe syndrome include joint swelling, arthritis, and benign growths called **fibromas** (especially on the feet and hands). These problems are particularly prevalent in the teenage and adult years. In some cases these problems can be quite severe and debilitating. The underlying cause is unknown and there is no effective therapy except treatment for pain.

3.5.6. Teeth

Many individuals with Lowe syndrome require extensive dental care. A high palate, small mouth, rickets, and other bone and metabolic factors often result in crowding, poor alignment, the susceptibility to decay, and delayed shedding of primary teeth. Many children require teeth extraction. A few have successfully worn braces. Dental cysts (sometimes called “eruption cysts”) appear to be quite common with teething but usually resolve after permanent teeth are in. Regular dental care should be started when the first baby teeth have erupted.

3.6. General Health Concerns

Lowe syndrome often gives rise to other, more generalized health concerns in addition to those previously discussed.

3.6.1. Conditions causing metabolic imbalance

Any circumstance which interferes with the ability of children with Lowe syndrome to take in their usual amount of daily fluids and medicines may increase their risk for developing metabolic imbalance. This is more likely to occur with illnesses such as **colds, flu, vomiting, or diarrhoea**. It may also occur when uncontrolled seizures interfere with normal fluid intake. At these times parents should seek prompt medical attention because intravenous fluids and medications may be needed.

Also, some children may need intravenous fluid and medication therapy to prevent metabolic imbalance when having surgery, anaesthesia, or other procedures which require a period without eating or drinking.

3.6.2. Respiratory illness

Children with Lowe syndrome may be more susceptible to developing pneumonia because of hypotonia (see “Hypotonia” in [Brain and Central Nervous System](#)) which may cause an inability to cough strongly and effectively. They should be monitored carefully during episodes of respiratory illness.

Parents may learn to administer postural drainage therapy, which may help to loosen mucous plugs in the lungs.

3.6.3. Eating difficulties

Hypotonia can affect the ability to suck and swallow, causing several potential problems including inadequate nutritional and fluid intake and inability to take medications. Also, poorly coordinated swallowing abilities can increase the risk for **aspiration pneumonia** (which can result when food or liquid goes down the trachea and into the lungs instead of down the oesophagus and into the stomach). Specialists in occupational or speech and language therapy may be able to provide “feeding training” to help improve the ability to suck and swallow. If a child is not able to take in his daily nutritional requirements, alternate methods of feeding may need to be considered. One method is the use of a **nasogastric (NG) feeding tube** which is placed through the mouth or nose into the stomach. The NG tube is not permanent. Another method is **the gastrostomy tube (G-tube or button)** which is surgically placed directly into the stomach through the abdominal wall.

Another common problem in Lowe syndrome is **gastroesophageal reflux (GER)** (causing acid indigestion) a condition often associated with hypotonia. In GER, the sphincter muscle at the top of the stomach does not stay shut, allowing food or liquids to come back up the oesophagus. This often causes heartburn, vomiting, and oesophageal irritation from stomach acid. It also causes an increased risk for aspiration pneumonia. To diagnose this condition physicians may order an upper GI series and a scinti-scan (X-rays with isotope) for reflux. Treatments may include adaptations such as eating upright and elevating the head of the bed, acid suppressing medications, and/or surgery.

3.6.4. Constipation

About one-half of individuals with Lowe syndrome have constipation. Poor muscle tone may contribute significantly to this problem. Some doctors believe, however, that constipation is a specific feature in Lowe syndrome and represents a direct effect of the gene upon the intestinal muscles, causing an inability to move the stool effectively.

Treatment includes adequate amounts of fibre in the diet and plenty of water. If dietary control is ineffective, medication may need to be considered. This should be done only under a doctor’s care. **Enemas are not recommended** because they can lead to serious metabolic imbalances that could be life threatening.

3.6.5. Cysts

Cysts, a common problem in Lowe syndrome, can occur in many places, including the mouth, kidneys, brain, and skin. Dental cysts appear to be quite common with teething but usually resolve after permanent teeth are in. In older boys with Lowe syndrome, cysts in kidney and skin appear to be more frequent. Cysts in the brain have also been reported.

In adults with Lowe syndrome, skin cysts around the lower back and buttocks can become quite painful and occasionally become infected. The cause of the cysts is not known, but it probably is a specific effect of Lowe syndrome.

Treatment with retinoic acid derivatives may be considered, but the potential negative effect on the kidneys is unknown.

3.6.6. Undescended testes

Undescended testes, or cryptorchidism, occur at birth in about one-third of the boys. The testes will descend naturally with time in about one-third of those affected. The remainder should be evaluated prior to 2 years of age to determine if surgical correction or other medical therapy is needed

3.6.7. Delayed Puberty

In some cases puberty can be delayed and some will need testosterone stimulation. The timing needs to be right and this should be discussed with an endocrinologist well in advance.

3.7. Prognosis

Although it is not possible to predict the future for any particular individual, some general observations can be made. With appropriate medical care, many of the problems associated with the syndrome can be treated effectively, allowing life expectancy to extend well into adulthood, with some young men living into their 30's and 40's. Progressive kidney failure (see "Kidney Failure" in [Kidneys](#)) appears to present a significant limitation on life span. However, deaths from complications of Lowe syndrome have occurred at all ages due to infection, dehydration and pneumonia. These estimates rely on current medical practice and may change significantly with more research and the advent of new treatments.

4. Genetics and the Molecular Basis of Lowe Syndrome

Summary:

- Lowe Syndrome is caused by a genetic mutation
- It can be inherited or it may arise spontaneously
- The affected gene codes for a protein called phosphatidylinositol 4, 5-bisphosphate 5 phosphatase which is involved in many functions in the body
- The condition affects only males as the gene is on the X chromosome (of which males have only one copy)

Lowe syndrome is a genetic disease, which means that the condition is caused by a defective gene. We inherit our genes from our parents – half from the mother and half from the father – they are the basic units of life. **Genes** are the ‘blueprint’ for the body. Each gene gives the information needed to make a component of the body. If there is an error in this information then the component will not be made properly and this may cause disease or disability. It’s a bit like trying to use a set of instructions to build a piece of furniture. A small mistake in the instructions may entail there is a wrong screw that affects the whole piece.

The body is made up of building blocks called ‘**cells**’. In a newly fertilized egg, all of the cells are the same and they are known as ‘**stem cells**’. As the egg develops into an embryo, the cells ‘differentiate’ and take on a particular role in the body e.g. there are skin cells, kidney cells, muscle cells, brain cells, etc.

Almost every cell in the body* contains a copy of the ‘blueprint’, the genes. To carry out their function in the body, each cell makes special molecules called **proteins**, which do all the work in the body, metabolizing food to make energy, breaking down toxins, enabling growth, regulating bodily functions, etc. The genes are the set of instructions used to make proteins. If there is a mistake in the set of instructions then a protein may not be made properly and this may lead to disease.

Before they have differentiated they are known as ‘stem cells’ as they have the potential to become any kind of cell. Once a cell has differentiated and taken on a function, it cannot change into another kind of cell.

4.1 How Can Genes Cause Disease?

Genes are made up of a material called ‘deoxyribonucleic acid’ or DNA. DNA is packaged into chromosomes. DNA is made up of lots of small units (bases) that form a long thread. There are 4 kinds of base, known as A, T, C and G. These 4 letters are the basis of the code that the genes are written in. Their order and number varies depending on the instruction – just like building up words from the alphabet. The words need to be in the correct order to make up a sensible instruction (i.e. gene). Thousands of these letters may make up the instruction for one protein. A mistake in just one of these letters can mean that the protein is not made properly – just as a small typo can make a word unrecognizable or converted into a different word altogether and render the sentence incomprehensible.

Lowe Syndrome occurs when there is a mistake in the gene for an enzyme (a kind of protein) called **phosphatidylinositol 4,5-bisphosphate 5 phosphatase**. This enzyme is involved in many metabolic pathways in the body and without it, several areas of the body are unable to function properly, causing disability. These include the eyes, brain, central nervous system, bones and kidneys . These effects are described in ‘Medical Features’.

‘Metabolism’ refers to the complex set of physical and chemical processes that maintain functions in every cell of our bodies and therefore sustain life itself. These processes are carried out by ‘enzymes’, special proteins that do all the work in a cell.

4.2. Mutations: How Does A Mistake in the Genetic Material Come About?

A defective gene is caused by a ‘**mutation**’ – a change in the DNA sequence of the gene. Most mutations of genes occur spontaneously, usually for unknown reasons. They may involve just a tiny part of the DNA in a gene. They are not caused by being exposed to drugs or alcohol or emotional events during pregnancy. Once a mutation occurs, however, it becomes “fixed” in a person’s genetic material. If that individual survives and grows up, he or she then has the potential to pass or transmit the altered gene to subsequent generations. Thus the disorder becomes hereditary in that family. There is no single common mutation in the LS gene. Different families may have different mutations.

4.3 Is Lowe Syndrome Always Inherited From the Mother?

No. There are two ways in which a boy might acquire Lowe Syndrome:

Inheritance:

Some cases of Lowe Syndrome occur when a mother has a faulty copy of the LS gene and passes it onto her son. By contrast, LS cannot be transmitted by a father. The mother does not show the symptoms of Lowe Syndrome, she just carries the gene – she is known as ‘carrier’ in genetic terminology. She may have inherited the gene from her mother or it may be a spontaneous mutation. She will not know that she is a carrier for the disease. Once a child with Lowe Syndrome is born into a family, the mother should be tested to see if she is a carrier as this may affect future pregnancies. Her female relatives can also be tested for carrier status to determine whether they are at risk of having a Lowe Syndrome child. Mutations are chance events and are not caused by any fault or action on the mother’s part, only bad luck.

Spontaneous Mutation:

At some point after fertilisation, there may be a spontaneous random event in the development of the embryo in which the LS gene becomes mutated and the child is born with the condition. Just as for any such disease, this is a random event that cannot be predicted and is not the result of any ‘fault’ on the part of the mother. If this is the case, the mother is no more likely to have a Lowe Syndrome child in subsequent pregnancies than any other woman but this can only be determined by testing to see if she is a carrier (see later).

4.4. Why Do Mainly Boys Get Lowe Syndrome?

The LS gene is found on the X chromosome – one of the two sex chromosomes. In humans, gender is determined by the sex chromosomes – boys are XY and girls are XX. An X chromosome is always inherited from the mother and either an X or a Y is inherited from the father, with a 50:50 chance each time i.e. for each pregnancy there is a 50:50 chance of having a boy or a girl.

Some diseases are known as ‘X-linked’ diseases, which means that they appear on the X chromosome. The Y chromosome is smaller than the X chromosome and does not contain as many genes. Boys have just one copy of the X chromosome, while girls always have two. This means that even if a girl has a faulty copy of the X chromosome, she has a working copy to compensate so she will not show the signs of the disease, although she may pass it on to her child. Boys do not have a second X chromosome and they therefore suffer the disease.

Since the early 1960’s, physicians have known that the gene causing Lowe syndrome is located on the X-chromosome.

4.5 What is the probability of a carrier having a Lowe Syndrome Child?

Women who are Lowe syndrome carriers have one X-chromosome with the normal gene and one X-chromosome with the Lowe gene. If they have a son, there is a 50:50 chance of him having Lowe Syndrome depending on whether he inherits the 'normal' X or the LS X chromosome. If they have a daughter there is a 50:50 chance of her being a carrier but she will not have the disease.

For each pregnancy, a woman who is a carrier has a 1 in 4 chance of having a child with Lowe Syndrome.

4.6 Gene Therapy

Gene therapy is used to supplement a defective gene with a working version. It is used to treat hereditary diseases in particular. The idea is that a 'normal' gene is introduced into cells to replace an 'abnormal' gene. The biology involved in human gene therapy is enormously complicated and it is in the very early stages. A major difficulty is delivering the working gene into the cells without disrupting any other genes or the working of the cell. Before gene therapy can be used effectively, techniques need to be developed and diseases need to be better understood. Lowe Syndrome affects a variety of different tissues in the body and the mechanisms of the missing gene are not fully understood. For this reason, it may be very difficult or even impossible for Lowe Syndrome to be treated with gene therapy – at least in the foreseeable future.

4.7 Genetic Counselling

If there is a case of Lowe Syndrome in a family, the female relatives of the mother may also be at risk of having a Lowe Syndrome child. As described above, Lowe Syndrome may either be inherited from the mother or be caused by a spontaneous mutation. In the former case, there is a possibility that other women in the family may also be carriers of the disease and therefore might be at risk of having an LS son.

Women who are at risk of being carriers include the mothers and sisters of affected boys, as well as the boy's maternal aunts and their daughters. Determining whether the mother of a Lowe child is a carrier is important for both her future pregnancies and those of her female relatives.

If she is not a carrier then the mutation that caused the syndrome was spontaneous (see previous section) and other family members are no more likely to be affected.

Couples who are at-risk of having an affected child with Lowe syndrome should explore their family planning options with the guidance of their physician and/or a genetic counsellor. Geneticists and genetic counsellors can help determine the chances of having an affected child.

4.7.1 Carrier detection

In some cases, a woman's carrier status can be determined from her family history. For instance, the mother of a son with Lowe syndrome is presumed to be a genetic carrier if there has been a previous case of Lowe syndrome in her family. If there were no other known cases of Lowe syndrome in the family, however, the mother of an affected boy might not be a carrier, since her son's condition could be the result of a new gene mutation.

In most cases, especially in women after puberty, carrier status can be determined by a slit-lamp eye examination performed by an ophthalmologist (a doctor specializing in diseases of the eye). The examination must be done with the pupils dilated (with eye drops). Approximately 95% of all carriers of the gene for Lowe syndrome have subtle changes in the lenses of their eyes, especially in the teenage and adult years. These changes, which appear as tiny dots and flecks in the lens in a characteristic distribution and pattern, typically cause no effect on vision and, if not looked for diligently, may be mistakenly dismissed as normal variations. Therefore, the geneticist should insist that the examination only be made by an ophthalmologist with experience with the subtle variations of the lens opacities of Lowe syndrome carriers.

If a reliable examination detects these characteristic lens opacities in an at-risk female of any age, then she is a carrier. If the opacities are not present in an adult female, she is probably not a carrier. This conclusion cannot be made with absolute certainty, however, especially if she is less than 15 years old.

There is no 100% reliable chemical or laboratory test to determine carrier status for all at-risk females at this time. However, genetic analysis may be possible for some family members (see V. Research).

4.7.2 Non and Atypical Carriers

When a careful eye examination of the mother of a child with Lowe syndrome is normal (that is, the characteristic lens opacities are not present), there are three possible explanations for the Lowe syndrome in her child.

First, and most commonly, the disease is the result of a **new genetic mutation** in

one of the mother's eggs. In this case, the mother is not a carrier and she is no more likely to have another child with Lowe syndrome than any other non-carrier female in the general population.

Second, and more rarely, she really is a carrier but falls into the group of 5% of all carriers who fail to show significant changes in their eyes. Her probability of having a child with Lowe syndrome is 25% with each pregnancy (50% for each male pregnancy) but the eye exam will not be able to determine whether this is the case. In this case, her female relatives are at risk of being carriers.

Third, and most rarely, the mother may be **mosaic** for the mutation in her ovaries. In this case, she may have additional eggs carrying the Lowe syndrome mutation without showing signs in the lenses of her eyes. Her risk of having another child with Lowe syndrome or a daughter who is a carrier would be much greater than that of the general population, but not the full risk that a true carrier female has (see Carriers).

Unfortunately, there is no reliable biochemical or molecular test to diagnose mosaicism. For that reason, even women with normal eye exams can be offered prenatal testing because of the risk of unsuspected mosaicism.

However, whether the mother of a child with Lowe syndrome is a non-carrier or is mosaic, her sisters or other female relatives (except for her daughters) are not at risk for being carriers because, in either case, the mutation occurred as a new genetic event in the mother herself.

4.7.3 Family planning options

At-risk couples have several options. Some may choose to "take their chances" with a pregnancy, while others may consider prenatal testing. Some couples may be interested in adoption or in techniques that would use a donor egg from a non-carrier female. Others may be interested in methods to increase their chances of conceiving a female since females, even if carriers, do not develop the disease.

If prenatal testing is an option, testing to determine if the foetus is male or female is a well-established procedure and is widely available. If the foetus is male, prenatal enzyme analysis identical to the test used to diagnose Lowe syndrome in patients is available. Enzyme analysis can be used for prenatal diagnosis even if carrier status has not been established firmly. It can also be used whether or not gene analysis has succeeded in identifying the family's specific gene alteration.

i. Prenatal testing:

Prenatal testing can be accomplished by one of two methods: CVS (chorionic villus sampling), which is done at 11-13 weeks, or amniocentesis, which is done at 15-18 weeks. Although the procedure itself can be performed in the local community, at the present time the analysis for the OCRL enzyme test can only be carried out at the Biochemical Genetics Laboratory in the Department of Molecular and Human Genetics at Baylor College of Medicine in Houston, Texas. For more information, please contact the Lowe Syndrome Trust. As with any prenatal diagnosis, the testing should be planned well in advance of the pregnancy.

ii. Pre-implantation Diagnosis:

An experimental technique called preimplantation genetic diagnosis has been suggested as another option for some couples. This technique involves in vitro fertilization and then testing the DNA in one cell of the fertilized eggs for the presence of a disease-causing gene alteration. Any embryo that is found to lack the disease-causing alteration (and by inference is normal) could be implanted into the womb. Preimplantation genetic diagnosis has been used successfully in a few genetic disorders but has not been tested rigorously in Lowe syndrome and therefore remains only a theoretical possibility. Preimplantation genetic diagnosis is a DNA test that would require accurate knowledge of the family's specific gene alteration. It cannot be used for the enzyme diagnosis for Lowe syndrome because the amount of material available for study is too small.

Many factors will affect a couple's family planning decisions, including their personal, family, ethical, and religious views, as well as financial, educational, and geographical considerations. Ultimately, the right decision for any individual or family is the one with which they are comfortable now and will remain comfortable with as they look back from the future.

5. Development and Education

This section looks at the development and educational needs of boys with Lowe syndrome develop. This does not pretend to be a comprehensive guide; children and families are all different, needs vary and, sadly, educational provision varies from area to area. This section gives an idea of the ‘toolkit’ of professionals that children are likely to need and some key areas that will need consideration.

Boys with Lowe syndrome are not all alike; the presence and severity of symptoms varies from child to child, even in the same family and the age of achieving major developmental milestones varies. However, we can make some general comments about the development and educational needs of boys with Lowe syndrome.

Boys with Lowe syndrome are usually significantly delayed in most areas of development because of the physical and mental effects of the condition. While development generally follows the normal sequence, the level of development in one area (language, for instance) may be more advanced than in another (gross motor skills, for instance). Various therapies and educational programs can help affected boys develop to their maximum potential.

In general, children with Lowe syndrome, even those with behaviour problems, are known to have “bubbling” personalities. They are loving and sociable and have a wonderful sense of humour. Many have a special feel for music. When healthy and in a stimulating environment, they are often happy and alert. With help, they can grow and develop into functioning members of their families and communities and can be enjoyed and appreciated for their unique personalities and accomplishments.

5.1. Infancy and Early Years

5.1.1 Early intervention

Research has proven that early intervention with disabled children and their families is both crucial and effective. If support and services are provided as early as the need is apparent, a child’s development will progress more quickly than if left unattended until age six or older.

5.1.2. Physical development

Infants with Lowe syndrome benefit greatly from physiotherapy. Some families arrange physiotherapy on a private basis. Some have access to infant intervention

programs provided by local services. Professional therapists can often train parents to carry out a therapy program in the home. In the early years goals may include holding the head up in a prone position, rolling over, sitting alone, and crawling. As in most areas, progress is usually slow. However, most affected boys will achieve these goals between a few months and five years of age.

5.1.3. Speech development

Delayed speech development is particularly frustrating for many parents and children during these years. Several factors contribute to delayed speech, including physical characteristics such as low muscle tone, vision impairment, high palate, and frequent illnesses; general learning difficulties that affect the understanding of word meanings, the ability to process and organize information, and the ability to use the information to communicate meaningfully; and environmental factors such as limited play and learning opportunities, minimal social activities, and limited ability to move independently around the environment.

Despite significant speech delays, most boys with Lowe syndrome will eventually be able to talk. By the age of 2?, most affected children can imitate words. By age seven, almost all can talk to some extent, and most can (at the very least) combine two words into a phrase. Many, in fact, eventually develop into very talkative individuals.

5.1.4. Eating problems

In some cases, the same factors that cause delayed speech may also contribute to eating problems. Poor muscle tone may result in reduced control of fine motor movement of the tongue, lips, and jaws that are necessary for sucking, swallowing, and chewing. As a result, some boys have difficulty making the adjustments from baby food to table food. An oral-motor treatment plan may be developed as part of the child's therapy program. By the age of five, the majority of children with Lowe syndrome are able to eat table food (see "Eating Difficulties" in Special Health Concerns). A speech and language therapist will be able to advise on all of these areas.

5.2. Middle Childhood and Adolescence

5.2.1. Walking

Generally, physiotherapy continues during these years, with an emphasis on walking and other gross motor skills. About 70% of boys with Lowe syndrome

learn to walk alone between five and thirteen years of age, with most having developed the skill by the age of seven.

5.2.2. Toileting and self-help skills

Toilet training can be quite challenging for boys with Lowe syndrome. Although many begin training in the earlier years (and a few succeed), the majority achieve this major milestone between the ages of five and thirteen, or even older in some cases. Some boys are toilet trained in the day-time but night time can be more difficult. The NHS have an incontinence team who may be able to advise. Constipation may complicate matters further.

Other self-help skills such as dressing and grooming may also be delayed. Most of the boys have great difficulty with fine motor skills such as tying shoelaces, buttoning buttons, and writing. Special adaptations such as Velcro fasteners and computers can help the children gain more independence.

5.2.3. Puberty

In general, puberty is slightly delayed in boys with Lowe syndrome, but otherwise follows a typical progression.

5.2.4. Behaviour

Some boys develop severe behaviour problems, especially during the school age years. As a result, parents and school staff may have to spend significant amounts of time and attention dealing with these problems because they can interfere with learning, social interaction, and family functioning. A behavioural psychologist may work with parents and teachers to develop appropriate and effective methods for dealing with the problems and helping the child to maximize his capacity for learning. Behaviour problems in Lowe syndrome are believed to have an organic origin. That is, they are caused by a problem in brain function due to the syndrome. As a result, parents and teachers may find it helpful to consider the behaviour problems as another one of the child's handicaps. Also, because medications are often helpful in treating the behaviour problems, a doctor may be involved in the treatment and educational plan.

The boys almost always exhibit behaviour on the autistic spectrum. Autism is a communication disorder that affects how people relate to the world around them. Children and adults with autism have difficulty with social interaction; they may find it difficult to make friends or understand what constitutes appropriate behaviour, often leading to serious behavioural problems. Autism is characterized by three main areas of difficulty (known as the triad of impairments):

- **Social interaction** – people with autism may appear indifferent to other people and unable to relate to them
- **Social communication** – they may have difficulty using verbal communication. They may also have difficulty with nonverbal communication such as reading facial expressions and body language
- **Imagination** – they may have difficulty developing appropriate interpersonal play skills

Autism is viewed as a spectrum disorder. It can range from relatively ‘high functioning’ people who have difficulty engaging with others or coping with daily interactions to those who may have serious behavioural and communication difficulties and may be aggressive towards themselves and/or other people. People with autism may appear to live in a world of their own and this can be incredibly stressful for families. They may have repetitive and limited patterns of behaviour and a strong resistance to changes in familiar surroundings and routines.

5.2.5 Education

The right education for boys with Lowe syndrome depends upon several factors, including the boy’s individual needs and community resources.

Children with Lowe Syndrome will have Special Educational needs (SEN) such as general learning difficulties and/or autistic spectrum disorder (ASD) require specialist education. Sadly, there is currently very little specialist education available; across the UK, there are about 7,500 places for the (minimum of) 90,000 children with autism. It has been shown that early intervention is the most effective way to enable children to learn appropriate behaviour and it is important for children to be assessed as early as possible to facilitate them getting appropriate education.

Children with Lowe Syndrome will need a Statement of Special Educational Needs (SEN). This is a legal document that lays out the details of Special Needs which the child has. The statement then goes on to outline the specific help that will be made available to meet the child’s Special Needs. This is called Special Educational Provision.

For information on Special Educational Provision in your area, contact your Local Education Authority. There are details of organisations who provide information on educating children with ASD in the ‘Contacts’ section of this booklet.

5.3. Adulthood

Throughout life, most boys with Lowe syndrome live at home with their families. Some families decide that placement in a residential setting is appropriate due to the complexities of medical management, educational needs, or severe behaviour problems. As adults, some individuals have successfully made the move into a group home while a few live independently. Some work in sheltered workshops or participate in other special programs for adults with disabilities. Parents should consider establishing legal guardianship of their son when he turns 18 years old.

6. Parents and Families: Living with Lowe

Raising a child can be a wonderful and challenging experience; raising a child with severe disability raises even more challenges but there will also be positive experiences along the way and this should not be forgotten. In this section, we will discuss how having a child with Lowe Syndrome may impact upon a family and offer some advice based on parents' past experiences. Every family is different and, although small, there is a network of families affected by Lowe who are there to share experiences with (see Contacts at the end of this booklet).

Lowe Syndrome presents many difficulties for families as the children not only have complex medical problems but also have Special Educational Needs (SEN). Parents will have to deal with complex medical problems, with an often-unfamiliar special education bureaucracy and with raising a child whose development is slow and erratic and whose behaviour may disrupt family life.

6.1. Diagnosis and early years

Parents usually learn that there is something wrong shortly after birth when their new born child is diagnosed with cataracts and likely hypotonia ('floppy baby' syndrome). As most doctors are not familiar with Lowe syndrome, many families (especially those with no history of Lowe syndrome) experience long and frustrating delays before receiving the diagnosis and the beginning of treatment of this rare and little known condition.

Not long after birth, the child is likely to need a cataract operation. In the first two years, regular tests are needed to pick up the onset of kidney problems. The stress of having a new baby, and having to deal with medical problems and the complications and uncertainties of diagnosis can be very difficult and it is important to develop strategies for coping with the emotional impact along with the immediate practical problems. The Lowe Syndrome Trust can help by supplying contacts for help and guidance and by providing information.

6.2. Growing Older

Boys with Lowe syndrome are often warm and loving but they can also be distant and rejecting. They are wonderfully curious but are given to exhaustive conversation. Often happy and cheerful, they can also be obstinate and forceful in trying to get what they want and can provoke a crisis at any moment and at any place. Their behaviour is on the autistic spectrum (see Education and Development) and their educational and daily needs can be extremely challenging.

Having a child with so many special needs places extra demands time, energy, and money. A family can easily become socially isolated and emotionally drained, focusing all its attention and energies on caring for the child. While parents continue to have emotional “ups and downs” over the years, experience helps them make the adjustments needed to meet the needs of their son, their family, and themselves. Experienced parents offer the following bits of advice to help new parents keep things in perspective and maintain a healthy and realistic attitude.

6.3. Advice for Parents

It is immeasurably useful for parents to become as knowledgeable about Lowe syndrome as they can. It may well be the case that they find themselves providing information to health professionals and care workers unfamiliar with the condition. Siblings will also need to understand their brother’s condition. They should know its name and that it is not contagious. As they get older they should be told how Lowe syndrome is inherited and the implications for their own children. If they are involved, extended family and friends should be given as much information as possible so that they can understand the child’s condition and be supportive. It is also important to seek professional advice and put developmental programmes such as speech and language therapy, physiotherapy and occupational therapy in place (where possible) to help your child’s development.

Remember that progress will be slow.

Listen to the concerns that other family members have and keep them informed. Involve the whole family in caring for the child if possible. If you have other children, help them to understand their brother’s condition and the extra attention that he needs but that this doesn’t mean you love them any less. Giving them opportunities to help can make them feel grown up and an important part of the family. Siblings can provide wonderful stimulation and companionship and, because of their unique perspective, are sometimes able to offer surprisingly helpful suggestions.

6.4. Support

Get to know other parents in the UK and international LSA. The LSA is a support group in the USA who produce a newsletter called ‘On the Beam’ and organise family conferences every other year (see ‘Contacts’). Although you may be separated by hundreds or thousands of miles, you can use the telephone, internet group, e-mail or regular mail, or share letters in On the Beam and even attend conferences.

Getting to know other parents who have children with disabilities or chronic illness can be very positive and an invaluable source of advice and support. In addition, a community group is a valuable resource in finding out about local programs and services.

Learn about the rights of people with disabilities. You can be your child's best advocate as well as an advocate for other children.

Understand that the many emotions you feel are normal, including grief, fear, anger, and despair. There is no right or wrong way to feel. What is important is how you choose to cope with your feelings. Fear and anger, for instance, can lead to paralysis or they can lead to productive action.

7. Research into Lowe Syndrome

Historically, there has been very little research into Lowe Syndrome as it is believed to be very rare although it is important to note that as yet there is no official clinical database giving numbers worldwide – the Lowe Syndrome Trust is seeking to address this. The lack of research projects is starting to change as the Lowe Trust raises funds to drive this forward.

This section gives a quick history of how research into Lowe has developed since its initial discovery and explains some of the difficulties associated with the research, current research directions and the work of the Lowe Syndrome Trust.

7.1 Early research 1952 - 1982

Lowe Syndrome was first recognised as a disease in 1952 by Drs. Lowe, Terrey, and MacLachlan at the Massachusetts General Hospital in Boston. In 1954 the specific form of kidney problems associated with the syndrome was recognized. X-linked inheritance was suggested in 1957, and the ability to identify female carriers by eye examination was confirmed in 1976. Research was held back as the biochemical manifestations of Lowe syndrome were found to be too nonspecific for easy investigation as the syndrome affects such a wide array of pathways. There was no single abnormal metabolite which would point to a specific pathway to investigate. Furthermore, there are no naturally occurring animal models for the disease. Researchers have been restricted both by the limitations placed on investigations using human patients, and a lack of human research subjects due to the rarity of the disease.

Significant progress has only begun in the past decade as several factors that have frustrated researchers' efforts over the years have changed. Lack of funding for research projects, lack of awareness, technical barriers to research and a lack of research subjects have all hampered research progress.

7.2 Developments 1983 - present

The general lack of research projects started to change in 1983 when the Lowe Syndrome Association (LSA) was founded in the U.S.A. Researchers now had access to a large pool of willing research subjects for the first time.

7.2.1. Identification of the genetic basis of Lowe Syndrome

The dramatic advances in the field of genetics during the past decade have opened new avenues of research and have led to significant advances in understanding Lowe syndrome. In 1995, it was discovered that Lowe syndrome is caused by a particular enzyme deficiency due to a defective gene. This

development has indicated clear avenues for research.

The first big step towards identifying the underlying defect took place in 1986 when Drs. Lewis and Nussbaum and their colleagues at Baylor College of Medicine succeeded in assigning the Lowe syndrome gene to a small region in the middle portion of the long arm of the X-chromosome. Subsequent work by many collaborating scientists ultimately culminated in identifying the exact identification of the gene in 1992. The gene site for Lowe syndrome is known as OCRL1. Three years later, Dr. Nussbaum and his colleagues, then at the National Institute of Health, announced the discovery that the defective gene causes a deficiency of an enzyme that is essential to inositol metabolism. The enzyme phosphatidylinositol 4,5-bisphosphate 5 phosphatase is essential to normal metabolic processes that take place in a part of the cell called the Golgi apparatus. Because this enzyme is deficient in Lowe syndrome, cell functions that are regulated by the Golgi are abnormal, leading to developmental defects such as cataracts and kidney and brain problems.

Research shows that the OCRL gene may also be implicated in other rare genetic diseases such as Dent's disease, a discovery that may shed light on the relationship between genetic mutations and clinical diseases.

7.2.2. Research into Cell Signalling

Current research is directed toward understanding how and why the enzyme deficiency causes so many difficulties. The role of phosphatidylinositol metabolism in normal Golgi function and in Lowe syndrome is being investigated extensively by researchers.

The defective OCRL enzyme in Lowe Syndrome means that carriers can not control levels of a molecule named PIP2, which in turns leads to development of the symptoms of Lowe Syndrome. PIP2 belongs to an important group of signalling molecules named inositol lipid phosphates, which are involved in pathways that malfunction in a number of other diseases, including some cancers, neurodegenerative disorders and heart disease.

This research is investigating the core underlying biochemistry of the disease and will lead to a better understanding of the disease, facilitating improved diagnostic tests, the development of an animal model and may possibly lead to a cure through the development of a drug that can replace the missing enzyme.

7.2.3. Development of Diagnostic and Carrier Tests

The development of diagnostic and carrier tests have also been the subject of recent and ongoing research projects. The discovery of the enzyme deficiency led

to the development of a simple and reliable diagnostic and prenatal diagnostic test. A biochemical test — a direct assay of the enzyme phosphatidylinositol 4,5-biphosphate 5 phosphatase — was initially developed in 1996 .The enzyme assay is now commonly used to diagnose affected patients as well as to carry out prenatal diagnosis.

Biochemical testing is not, however, effective for carrier detection. For laboratory carrier testing, the specific change (mutation) in the DNA sequence that causes the disease can be used to identify carriers. To date, over 65 different mutations have been found in patients with Lowe syndrome. Thus, most families typically have a mutation unique to their family. DNA sequencing is the only way to establish which mutation is responsible for a particular case of Lowe Syndrome. Once the mutation has been identified, other female relatives can be tested for carrier status if this is needed.

This type of genetic mutational analysis is currently still an expensive procedure not commonly available through routine clinical laboratories. In some families with a strong family history of Lowe syndrome, DNA markers near the mutant gene may be used to trace the inheritance of the abnormal gene in the family without knowing the specific mutation in the gene. This approach, called “linkage,” is carried out by specialized genetic diagnosis labs. The eye examination of at-risk females (see “Carrier Detection” in IV. Genetics) currently remains the standard method for determining carrier status. However, an applied research project currently underway at the National Institutes of Health and funded by the Lowe Syndrome Association is directed towards streamlining and improving the process of searching for mutations. The LSA hopes that this project will lead to the development of a simple and reliable carrier test that will be available in clinical settings within the near future.

7.2.4. Clinical research

Researchers at the National Institutes of Health in the U.S.A. studied clinical i.e. medical aspects of the syndrome in a large number of individuals over a span of several years during the 1980's and early 1990's. Their discoveries led to a better understanding of the natural course of the syndrome and better treatment techniques for many of the problems. Other important research projects include a study that helped to establish a causal link between the syndrome and behavioral problems. Much work remains to be done in the area of clinical research.

Research projects are currently underway to investigate Lowe cataracts and kidney problems.

The Lowe Syndrome Trust (UK) is currently working on establishing a clinical database, which can be used by researchers to aid their work in both molecular and medical fields.

7.2.5. Brain and Tissue Bank

In the USA, the LSA supports research is by encouraging its parent members to register with the Brain and Tissue Bank (BTB) for Developmental Disorders at the University of Maryland. The BTB collects relevant tissues after surgery or after death and stores them for future research purposes. Supported by the National Institute of Child Health and Human Development, the BTB is dedicated to the “improved understanding, care and treatment of developmental disorders.” LSA families are encouraged to consider registering with the program.

The Lowe Trust in the UK is working to establish a similar bank to aid research.

7.3. The Lowe Syndrome Trust and Research

Good medical research requires a partnership between scientists, physicians and affected families. Cooperation and sharing of ideas has led to rapid advances in understanding the cause of Lowe syndrome and may lead to more effective therapies. By providing funds for medical and scientific research, the LST helps to encourage innovative thinking and interest in a rare condition that otherwise might go unnoticed. LST also organizes an International Symposium every two years – an opportunity for researchers to come together to share their work, learn from each other and stimulate future research.

The LST has set up a Scientific Advisory Board comprising expert biomedical researchers who assess research proposals put forward by researchers seeking funds to work on Lowe Syndrome.

One research project tends to lead to another as knowledge increases and new areas for investigation are developed. Although there have been dramatic advances in the understanding of Lowe syndrome during the five decades since it was first recognized, there is much that remains a mystery. With advances in medical and scientific technology and with the strong support of the LST, the future will undoubtedly see researchers finding more answers to the many profound and baffling questions that remain. For further details of current research projects, please contact the Lowe Syndrome Trust.





**Our Thanks to the
Big Lottery for funding this booklet.**



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