The Lowe Syndrome Trust has also funded three Lowe Syndrome Trust International symposiums at The Royal Society, London and The American Cell Biology Conference, San Diego, USA.
1. What is Lowe Syndrome?
Lowe Syndrome (LS) is a rare genetic condition that causes physical and mental handicaps and medical problems. Also called oculo-cerebro-renal (OCR) Syndrome. It was first described in 1951 by Dr. Charles Lowe and colleagues. In some cases Lowe Syndrome is the result of an original mutation and the mother is not the carrier.

2. What causes Lowe Syndrome?
Lowe Syndrome is caused by a defective gene that results in the deficiency of an enzyme called phosphatidylinositol 4,5-biphosphate. This enzyme is essential to normal metabolic processes that take place in a certain part of the cell called Golgi apparatus. Because of the enzyme deficiency, cell functions that are regulated by the Golgi are abnormal, leading to various developmental defects including cataracts, kidney and brain problems. How the enzyme deficiency leads to these defects is not yet completely understood.

3. What are the common features of Lowe Syndrome?
- Cataracts in both eyes, found at birth or shortly after
- Glaucoma (in about half of cases)
- Poor muscle tone and delayed motor development
- Mental impairment, ranging from borderline to severe
- Seizures (in about half of cases)
- Severe behavioural problems (in some cases)
- Kidney involvement (“leaky” kidneys or renal tubular acidosis)
- Short stature
- Tendency to develop Rickets, bone fractures, scoliosis and joint problems
- Short life span due to progressive renal failure, seizures and other causes: life expectancy may increase in the near future as knowledge increases
- Arthritis (swelling of the joints)
- Respiratory Illness
- Cysts
- Undescended testicles
- Constipation
- Tooth decay

4. What are boys with Lowe Syndrome like?
Generally, they are affectionate and sociable, love music and have great senses of humour.

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

6. What about Research?
In 1992 the gene that causes LS was found. In 1995 researchers discovered that the missing gene defect causes an enzyme deficiency. Researchers are continuing to investigate the function of the gene and the complicated biochemistry and cellular mechanisms of LS. Other areas that researchers have investigated in recent years include behaviour problems and clinical care. The Lowe Syndrome Trust was founded in June 2000 with an aim to fund Lowe medical research which will hopefully lead to better treatments and eventually a cure for the disease.

7. Can Lowe Syndrome be prevented?
In families in which a case of LS has occurred, a special eye examination can help determine carrier status of at-risk females. Research currently underway may lead to a more definitive genetic test for carrier status. Various family planning planning options are available, including parental testing. Families should consult with a geneticist to learn more about their options.

8. Where are diagnostic tests done?
To diagnose Lowe Syndrome within the UK, a DNA test can be requested via a consultant from Dr Andrew Wallace at St Mary’s Hospital Regional Genetics Services, Manchester. A skin sample can also be taken and sent to the Biochemical Genetic Laboratory at Baylor College of Medicine in Houston, Texas. Prenatal diagnosis is also provided at this laboratory. Physicians and families should contact the Lowe Syndrome Trust to find out further information on these tests.

9. How can I learn more?
Contact the Lowe Syndrome Trust for a copy of the Living with Lowe Syndrome: A guide for Families, Friends and Professionals. Single copies are free. More information can be found on the LST website www.lowetrust.com

10. How is Dens syndrome linked to Lowe Syndrome?
Please read attached information sheet.

Lowe Syndrome is a devastating genetic disease that affects thousands of little boys born with cataracts (either blind or partially sighted), stunted growth, poor muscle tone, rickets, scoliosis, arthritis (some never walk), kidney problems and mental impairment. In spite of these handicaps the little boys have extremely happy and cheeky personalities. Sadly, few survive to become adults. Yet today, it may be within our grasp to help cure this disease. The Lowe Syndrome Trust is a registered charity, founded in June 2000 as the only UK charity to raise money for medical research to cure this disease. With your help, we can be one step near to a cure.

MEDICAL AND SCIENTIFIC ADVISORY BOARD

ABOUT THE LOWE SYNDROME TRUST

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Lowe Syndrome and Dent Disease: two ends of a spectrum – May2012

The symptoms of Lowe syndrome and Dent’s disease overlap, with similar kidney disorders.

Lowe syndrome symptoms affects multiple organs, involving the eyes, kidneys, muscles and brain, while Dent’s is mostly restricted to the kidneys. Dent’s disease is classified as either Dent’s-1 or Dent’s-2, where Dent’s-1 is usually due to CLCN5 gene mutations and Dent’s-2 is caused by mutations in OCRL1, which is the same gene that is mutated in Lowe Syndrome.

Renal tubular acidosis needing medication, aminoaciduria and renal failure are more prevalent with Lowe. Patients with Dent-2 may also have mild developmental delay, elevated serum muscle enzyme levels and cryptorchidism, features typically seen in Lowe syndrome, demonstrating a continuous spectrum of symptoms and severity between Lowe and Dent-2.

Lowe syndrome patients’ growth is shorter compared with Dent’s. While Dent’s-2 patients are taller than those with Lowe, they are shorter than those with Dent’s-1, and can also have mild cataracts and mental retardation, like with Lowe.

To further investigate Dent’s Syndrome, in May 2012, the Mayo Clinic in USA established a Registry database to collect medical information on Dent Disease Patients.

References:


Ocr1 (INPP5F gene) antibody is available: http://www.antibodyresource.com/search/ Antibodies/63a25651-363e-5094-b964-ac1ce0243683/OCRL1

INPP5F Antibodies
Found a total of 24 INPP5F antibodies from 10 antibody suppliers. Human, mouse and rat.

Alternative protein names:
Inositol polyphosphate 5-phosphatase OCRL-1 / Lowe oculocerebrorenal syndrome protein / OCRL / OCRL1 / Q01968
http://www.nature.com/nri/focus/therapeuticabs/index.html

May 2012 Clinical trials register for Dents Patients http://clinicaltrials.mayo.edu/clinicaltrialdetails.cfm?trial_id=101556&eKeyword=dent
LOWE SYNDROME AND DENTS DISEASE

The discovery of a common genetic basis for two apparently different conditions, Lowe syndrome and Dent’s disease both related to OCRL1, has blurred the distinction between these two diagnoses. This leaflet describes the two diseases and tries to explain the differences and commonalities.

Lowe syndrome: In medical language, a syndrome is a combination of symptoms, which occur together and thus presumably have a common origin. In 1952, Dr Charles Lowe, a paediatrician in Boston, together with colleagues first described three boys with a combination of specific kidney, eye and brain symptoms, which we now call Lowe or oculo-cerebro-renal syndrome, which denotes the medical terms for eye, brain and kidney, respectively. The boys described by Lowe were all noted in infancy to have cataracts (a clouding of the lens in the eye), glaucoma (increased pressure in the eye), decreased intelligence and a loss of certain substances in the urine, that led to the development of rickets and an excess of acid in the blood. As more patients with this constellation of symptoms were identified it was recognised that it occurred in families and thus was likely due to a genetic problem. Moreover, all affected were male, whereas women apparently could pass on the genetic problem, but were not obviously affected by the disease, suggesting that the genetic problem was located on the X-chromosome (women have two X-chromosomes, so a mistake in one of them can often be compensated for by the other one, whereas men have an X and a Y-chromosome. Since the Y-chromosome carries a different set of genes, it cannot compensate for mistakes on the X-chromosome). In 1992, the gene underlying Lowe syndrome was identified and was called OCRL (for Oculo-Cerebro-Renal syndrome of Lowe). This made an accurate diagnosis feasible in boys suspected of having the disease by looking for mutations (mistakes) in the gene. Careful observation of affected boys revealed that there was a spectrum of severity of symptoms: some had severe eye manifestations, noted straight away at birth that required multiple surgical interventions yet still could lead to blindness; others had only mild abnormalities detected later in life on specific testing. Similarly, some boys have severe mental retardation, whereas others have borderline or normal intelligence. Aggressive behaviour and temper tantrums are noted frequently in patients with Lowe syndrome, but appear to be absent or only mild in some. With respect to the kidney, some boys have severe wasting of substances, such as calcium, phosphate, bicarbonate, amino acids and small proteins, that untreated lead to severe rickets and an excess of acid in the blood (the medical term for which is acidosis), whereas others exhibit wasting only of calcium and small proteins and do not require treatment. Some show deposition of calcium in the kidney on an ultrasound scan, or even stones, whereas others have normal appearing kidneys. Moreover, some patients show a progressive decline in the amount of blood processed by the kidney (Glomerular Filtration Rate or GFR), whilst in others this remains stable until well in adulthood. The reasons for the variability are unclear.

Dent disease: In 1964, Dr Dent and a colleague in London described two men affected by rickets in childhood associated with wasting of phosphate, calcium, amino acids and small proteins. In addition, they had a decreased GFR (see above). Interestingly, one of the two men described also had decreased intelligence. With time more descriptions of patients affected by similar symptoms emerged, many of them developing kidney stones and renal failure. As in Lowe syndrome, the disease affected exclusively males, occurred in families and could be passed on by women, who showed no obvious symptoms. In 1996, it was shown that mutations in a gene on the X-chromosome called CLCN5 could cause Dent disease. However, it was also noted that in about a third of patients with the clinical diagnosis of Dent disease no mutation in this gene could be found, suggesting that other genes could also cause Dent disease. In 2005, careful studies in one large family showed that all affected men had a mutation in OCRL, the gene associated with Lowe syndrome. Mutations in OCRL were then also found in some other patients with Dent disease. These patients are now often referred to as having Dent2 disease to distinguish them from patients with mutations in CLCN5 (Dent1 disease).

Lowe syndrome and Dent disease: two ends of a spectrum

The surprising finding of OCRL mutations in some patients with Dent disease has prompted the question, of how mutations in one gene, OCRL, can cause two apparently distinct diseases: Lowe syndrome in some, Dent disease in others. Clinical observations, however, suggest that the two diseases may be closer to each other than originally thought: several of Dent2 patients have reduced or borderline intelligence, and, in fact, this had already been noticed by Dr Dent in one of his original two patients. Nevertheless, other patients with Dent2 disease have normal or even above average intelligence. When looking at large cohorts of patients with Dent1, Dent2 or Lowe syndrome, it was noted that average growth is more compromised in Dent2 patients than those with Dent1, but less than in Lowe syndrome (Note: individual Dent2 patients can have perfectly normal growth, but the average of all Dent2 patients is less than normal). Both Dent2 and Lowe patients typically show elevated levels of certain muscle proteins in their blood, suggesting that muscle may also be mildly affected in both diseases. Considering also the variability of severity of symptoms in Lowe syndrome (see above), it becomes apparent that there is no clear distinction between Dent2 disease and Lowe syndrome. Whereas Dent1 disease only affects the kidney, the spectrum of symptoms in Dent2 disease can range from apparent exclusive kidney manifestations to involvement of other organs, notably brain and muscle in overlap with Lowe syndrome. Thus, the distinction between the two diagnoses rests mostly on the presence of eye abnormalities. When considering that this can occasionally be quite mild in Lowe syndrome, the distinction becomes somewhat arbitrary in those patients.

Nevertheless, in most patients with OCRL mutations the clinical diagnosis is clear: those boys with the typical eye, brain and kidney abnormalities are diagnosed with Lowe syndrome, whilst those with (almost) exclusive kidney problems have Dent2 disease. Yet, we do recognise that there is a fluid border between the two diagnoses. Perhaps this can actually help to identify treatments for Lowe syndrome: if we could find out why some patients seem to have only kidney problems with OCRL mutations and not the full spectrum of Lowe disease, this might provide clues for the treatment of symptoms in eye and brain.