The Lowe Syndrome Trust International Symposium

Molecular and Clinical Advances in Lowe Syndrome

The Royal Society, London
December 14th 2012

"Care today … cure tomorrow"
LOWE SYNDROME TRUST

The 4th International Symposium of the Lowe Syndrome Trust
'Molecular and Clinical Advances in Lowe Syndrome'
Royal Society, London, 14th December, 2012

The 4th International Lowe Syndrome Trust Symposium was held, as in previous years, at the prestigious location of the Royal Society in Pall Mall, London. The day comprised a series of talks by investigators studying various aspects of Lowe syndrome and the related Dent disease.

The symposium started with a moving account of the devastating consequences of Lowe syndrome from the mother of a boy that had sadly recently passed-away. It certainly brought home the importance of the research being done to better understand the disorder that will hopefully lead to better treatment and ultimately a cure for both Lowe and Dent's. The scientific talks started in the morning with an excellent presentation from Professor Joris Veltman from the Nijmegen Medical Centre in the Netherlands on how next generation DNA sequencing is revolutionising the field of genetic medicine. He presented several examples of how this technique is leading to improved understanding of the mechanisms underlying intellectual impairment in humans. The next talk was from Professor Helen Cross from the University College London (UCL) Institute of Child Health at Great Ormond Street Hospital, who gave an overview of the seizures and brain cysts that have been reported in Lowe syndrome boys, and what the possible mechanisms underlying these defects may be.

The next four presentations focussed on the kidney, which is a major affected organ in both Lowe syndrome and Dent disease. The first of these presentations was from Professor Robert Kleta, also from UCL, who described renal Fanconi syndrome, a defect in renal tubular function similar to that seen in Lowe and Dent's. Professor Kleta gave an interesting account of his team's discovery of a novel genetic cause for Fanconi syndrome in an African American family. He then went on to discuss the various cellular mechanisms underlying Fanconi syndrome. Professor Daniel Bichet from the University of Montreal discussed how water balance is controlled by the kidney, and how defects in this process can lead to human disease. Professor Steven Scheinman from The Commonwealth Medical College, in Pennsylvania, followed with a thought-provoking presentation on how the hypercalciuria (elevated calcium in the urine) observed in both Lowe syndrome and Dents disease may be brought about. Professor Scheinman described hypotheses involving both uptake of calcium from the intestine and its handling in the renal tubules. Dr John Lieske from the Mayo Clinic in Minnesota, USA, gave a very informative overview of the rare disease clinical research network initiative, highlighting progress made with the Rare Kidney Stone Consortium (http://www.rarekidneystones.org/), whose purpose is to ensure collaborative exchange of information on rare causes of kidney disease, including Dent disease, amongst patients, clinicians and scientific investigators. Consortia such as the Rare Kidney Stone Consortium are making a huge difference to our collective understanding of rare diseases.

The last talk in the morning was from Debbie Jacobs, the president of the Lowe Syndrome Association USA, who gave an account of the impressive work done by the LSA. Mrs Jacobs described the comprehensive survey of Lowe patients' symptoms that was undertaken in 2008, which has provided an extremely valuable source of information not only for the families of Lowe and Dent disease boys, but also interested clinicians and researchers investigating these disorders. It is clear that this survey provides a wealth of detailed insights into the manifestations of Lowe and Dent disease.

The talks in the afternoon concentrated more on the cellular and molecular mechanisms of Lowe syndrome and Dent disease. The first presentation was by Dr Claudio Aguilar from Purdue University in the USA described recent studies on how the protein mutated in Lowe syndrome and the Type 2 form of Dent disease, called OCRL1, functions in ciliogenesis, the formation of antennae-like structures called cilia that protrude from most cells in our body. Defects in cilia formation or function give rise to a number of diseases called ciliopathies, and Dr Aguilar proposed that the symptoms of Lowe syndrome and Dent-2 may arise through defective cilia function and consequently that these disorders should also be classified as ciliopathies. Next, Professor Martin Lowe from the University of Manchester, UK, described studies on OCRL1 and its role in protein trafficking, which may contribute not only to defects in cilia formation but also to the other manifestations of Lowe syndrome and Dent-2 disease. Professor Lowe is currently testing this hypothesis using a zebrafish model for both disorders. An important role for endocytosis in Lowe syndrome and Dent-2 disease was further supported by the presentation of Dr Tim Levine, from the UCL Institute of Opthalmology. Dr Levine convincingly demonstrated that loss of OCRL1 causes severe defects in cell polarity, an important feature of many cell types including those in the kidney and brain. He went on to show abnormal trafficking of cell polarity determinants suggesting this is the primary cause of defective polarity formation. Dr Laura Swan, from the group of Professor Pietro de Camilli at Yale University School of Medicine in the USA, described interesting work looking at new interaction partners for the OCRL1 protein. Using slime mould as a model organism, Swan and colleagues could identify three new partners for OCRL1 including one that is also present in humans, revealing new insights into how OCRL1 might function in trafficking in all species.

The presentation by Dr Rudger Woscholski from Imperial College London described the latest progress in the design of compounds that can sequester the lipid PIP2, which abnormally accumulates in cells when OCRL1 is absent or not functional, as in the case of Lowe syndrome and Dent-2 disease. Excitingly, one of these compounds could not only sequester PIP2, but also reverse many of the cellular defects that arise due to PIP2 accumulation. These promising results suggest the compound, or derivatives thereof, have utility as a possible treatment for Lowe and Dent-2 disease. An added benefit is that these compounds are also likely to be extremely useful as tools for studying the biology of lipid metabolism.

The final presentation of the day was the plenary talk by Professor Roland Baron from Harvard Medical School. Professor Baron gave an overview of bone remodelling, and described the most recent advances in our understanding of this fascinating process. This included exciting progress in the development of new therapeutics to treat bone defects such as osteoporosis. Lowe syndrome and Dent disease patients suffer significant skeletal abnormalities, which are thought to arise downstream from the primary renal tubular defect. However, Professor Baron raised the point that OCRL1 may directly participate in bone remodelling and maintenance, and studying this currently neglected aspect of OCRL1 function could prove fruitful. It is certainly possible that loss of OCRL1 could affect the skeleton both directly and indirectly.

This was the 4th Lowe Syndrome Trust Symposium. As in previous years, it was striking how much progress is being made in our understanding of the underlying causes of Lowe syndrome and Dent disease. This rapid progress is in no small measure down to the funding provided by the Lowe Syndrome Trust in the UK and Lowe Syndrome Association in the USA which has allowed researchers to concentrate on advancing our knowledge of these devastating conditions. Hopefully this progress will continue, which will not only increase our understanding but ultimately lead to possible treatment of both conditions.

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