Rare Diseases Day: targeting unknown diseases in children

There are thousands of families coping with the challenge of caring for a child with a rare disease. It is estimated that 3.5 million people in the UK are affected by a rare disease at some point in their lives[1]. Sadly more than 50% of those with a rare disease are children and young people and 30% of those with a rare disease will die before they reach the age of five[1].

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The children's charity Action Medical Research marked the annual global Rare Diseases Day on 28 February 2014 by announcing vital research breakthroughs and continuing investment into diseases for which there are often no cures. The charity aims to make a difference through medical research by tackling premature birth, treating sick and vulnerable babies, helping children affected by disability, disabling conditions and infections, and targeting rare diseases that together affect many children. Research is the key to saving many of these children from a lifetime of suffering and Action Medical Research is currently funding more than 14 different studies targeting rare diseases, including:

- Jeune syndrome
- medulloblastoma (a type of brain tumour)
- startle disease
- ataxias
- primary ciliary dyskinesia (PCD)
- brittle cornea syndrome
- mitochondrial disease
- Sanfilippo IIB
- argininosuccinic aciduria (ASA)
- liposomal storage diseases
- X-linked lymphoproliferative disease (XLP)
- Duchenne muscular dystrophy
- Smith-Lemli-Opitz syndrome.

Smith-Lemli-Opitz syndrome: working towards a new treatment

At least one in 60,000 newborn infants in the UK has the rare genetic disorder Smith-Lemli-Opitz syndrome (SLOS)[2]. All of these infants have autism spectrum disorders and the most severely affected have birth defects, such as cleft palate, scoliosis, learning disabilities and life-threatening heart defects. There is no cure and no proven effective treatment and it is thought to be the cause of a high number of miscarriages in Europe.

Case study

Brothers Alex and Daniel have both been diagnosed with SLOS. Alex was born with scoliosis, requiring major corrective surgery. As a baby he barely slept: he vomited every two to three hours a night and didn't grow much during his first six months. When Daniel was born, he had similar problems and had a hole in his heart. At just one day old he needed heart surgery, followed by further operations at three months and two years of age.

SLOS results from a failure of the body to make its own cholesterol. Recent discoveries suggest that two drugs might benefit children with SLOS. Dr Emyr Lloyd-Evans, of Cardiff University, is investigating this possibility supported by funding from Action Medical Research. "We have recently discovered similarities between SLOS and another rare illness called Niemann-Pick C (NPC)," explains Dr Lloyd-Evans. "In NPC, cholesterol gets stuck inside a compartment within cells called the lysosome. We think that the same thing happens in SLOS, meaning therapies that work for children with NPC might also help children with SLOS. Treatment slows disease progression of NPC – if it could do the same for children with SLOS that would be a significant advance. Our laboratory work will provide the essential proof of principle that's needed before clinical trials can begin in children with SLOS."

Brothers Alex and Daniel.

Primary ciliary dyskinesia (PCD): new improved testing

Previous research funded by the charity has recently resulted in some exciting breakthroughs in PCD. Children with PCD have abnormal cilia – tiny hair-like projections, which line the airways and ears. In PCD, the cilia do not perform their function of beating rapidly to sweep germs and dust out of the lungs. There is no cure for PCD, but the earlier a child's illness is diagnosed, the sooner the most appropriate treatment can begin and the better their quality of life.

Dr Hannah Mitchison, of the Institute of Child Health, London, was awarded a two-year research grant by the charity in 2010 to hunt for genes for PCD. Each year in the UK, over 100 children are diagnosed with this condition[3,4]. They suffer lifelong problems with recurrent ear and chest infections causing declining lung function and irreversible damage.

Case study

Kylie was born one month premature. She did not need neonatal care but not long after birth, her parents noticed that she produced a lot of phlegm and often had trouble breathing. When Kylie was eight weeks' old, her breathing became very laboured and she had a high temperature. Her symptoms worsened; an X-ray revealed she had pneumonia and she spent a week in hospital in isolation. For the first 18 months of her life, Kylie was in and out of hospital with high temperatures and breathing problems. She also had problems with her hearing and pain due to an infection of the middle ear. Kylie was over two years of age when PCD was diagnosed.

Dr Mitchison and researchers from the Molecular Medicine Unit and General and Adolescent Paediatric Unit, Institute of Child Health, London, were awarded a two-year grant from Action Medical Research in 2010. The team studied the DNA of 24 children with PCD from 11 different families. The children's parents and siblings also took part. The children all had abnormalities in specific components of cilia, called radial spokes. They were hunting for the genetic changes that cause these abnormalities.

Dr Hannah Mitchison.

Currently diagnosis of PCD is complicated, unpleasant and often lengthy. It sometimes goes undiagnosed or is mistaken for other illnesses such as cystic fibrosis or asthma, which cause similar symptoms.

Recent results from Dr Mitchison's research are the foundation of new improved testing techniques, which are already in use. She and her team uncovered mutations in four new genes – *CCDC39, CCDC40, RSPH3* and *CCDC164*[5]. Research has already identified genetic mutations that cause PCD in nine different genes. However, only around 40% of children with PCD have one of these mutations[6].

Results have led to the development of a new 'gene panel' type testing of more than 20 PCD genes. This will reduce the need for children to visit specialist centres for unpleasant tests, such as biopsies of the lining of their nose. Early diagnosis can relieve suffering by giving children access to treatment that eases symptoms, slows disease progression and protects the lungs from permanent damage.

Jeune syndrome: important genetic discoveries

Dr Miriam Schmidts, also from the Institute of Child Health, was awarded a three-year Research Training Fellowship by the charity in 2011 to investigate Jeune syndrome. An estimated 600 people in the UK, 69,000 worldwide, have this rare, incurable genetic condition[7-9].

Case study

At her 20-week pregnancy scan, Joshua's mother was advised that her unborn son appeared to be affected by some form of dwarfism, with legs and arms much shorter than expected. Nearly a month after Joshua was born, tests revealed that he had Jeune syndrome, a rare and incurable hereditary condition. Infants with Jeune syndrome are born with short arms and legs and an unusually narrow ribcage, which can restrict the development of their lungs causing severe, sometimes fatal, breathing problems. Problems with their liver, kidneys or eyesight, for example, are common and some children are born with more than five fingers or toes. From birth, Joshua struggled with breathing problems. Gradually the condition got worse: he endured two major invasive chest surgeries and even now needs a ventilator to help him breathe during the day and night.

Joshua with his parents and older brother Ethan.

Jeune syndrome is poorly understood, which has severely limited treatment options. Evidence suggests people with Jeune syndrome have dysfunctional cilia and that cilia play an important part in skeletal development. Researchers have already identified some genetic changes that can cause Jeune syndrome, but estimates suggest only a minority of sufferers carry these changes[10]. Dr Schmidts and her team have discovered new genes causing Jeune syndrome. In her research, Dr Schmidts sequenced

the DNA of children with the disorder, along with the DNA of their parents and siblings as a comparison. She also investigated the underlying disease processes involved in Jeune syndrome at the molecular level in a laboratory model and the role of the gene *DYNC2H14* in detail, focusing on any affect it may have on cilia.

Dr Schmidts and co-authors from Australia and the US, have revealed the links with Jeune syndrome and three genes known as *WDR60, WDR34* and *IFT172*[11-13]. Dr Schmidts is determined to help people with the condition by searching for more genetic changes that cause it. She hopes to improve diagnosis, boost access to genetic counselling and work towards new treatments.

Action Medical Research plays a vital role as the leading UK-wide medical research charity dedicated to helping infants and children. It continues to fund some of the best medical research in the world. Around one in nine babies born in the UK needs some form of special care at birth as a result of a difficult birth, a life-threatening condition or because they were born too early. The charity aims to reduce the high rate of premature birth, prevent pregnancy complications that threaten babies' lives and find the best ways to care for sick and vulnerable babies. It is also investing in new and better ways to treat babies following a difficult birth or a life-threatening condition such as hydrocephalus or congenital diaphragmatic hernia.

The Action Medical Research website has further information about the research it funds (www.action.org.uk/our_research). If healthcare professionals or their patients are affected by the conditions discussed here, the Jeune Syndrome Family Foundation (www.jeunes.org.uk) and the PCD Family Support Group (www.pcdsupport.org.uk) can be contacted for advice and support.

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