Why does neurodegeneration occur in Langerhans cell histiocytosis?

Project title: The origin of neurodegeneration in Langerhans cell histiocytosis

Lead researcher: Professor Matthew Collin, Newcastle University

Project Stage: Starting soon (January 2024)

Funded by: Jack's Journey, The Isobel Parmenter Memorial Fund, #TeamNimmy, and Danny's Dandelion Appeal

ABOUT THE PROJECT

Around one in ten children with multi-organ Langerhans cell histiocytosis (LCH) develop a condition where their nerve cells slowly stop working and die. This is called neurodegeneration, and it has no treatment. Neurodegeneration first occurs about three to 10 years after diagnosis, and can cause both intellectual and physical disabilities.

Scientists have come up with two competing theories to why this condition occurs. In the first, they suggest that the immune system cells with the LCH mutation enter the brain during a baby's first weeks of life. Immune cells are required for normal brain development but, if they are mutated, these cells could act like 'sleeper agents' that reactivate many years later. The second theory is that the mutated immune cells enter the brain only when the child becomes ill with LCH, occurring much later in their development. In this theory, the immune cells are 'rebels' that were allowed into the brain due to inflammation.

Deciding between these theories would have important implications for patients. If neurodegeneration is caused by sleeper agents, then doctors should prioritise treatments that preserve the healthy brain and avoid any drugs that might cause damage. If neurodegeneration is caused by the rebels, then doctors should clear the bone marrow and blood of mutations as quickly as possible, to prevent the rebel immune cells entering the brain. This might mean increasing the strength of current treatments.

Professor Matthew Colin, Newcastle University, wants to find out which theory is correct. In this project, he will be looking at patient blood samples to find when the LCH mutation first occurs. His team will grow individual stem cells from patient blood and bone marrow samples into separate colonies. As stem cells divide, they accumulate harmless mutations over time which can be used as a reference to compare other mutations to. When the researchers sequence the

genome of each colony, they can use these harmless mutations to look back in time and 'date-stamp' when the LCH mutation first occurred.

If the mutation is tracked to a very early stage of development, then it could have generated the sleeper agent immune cells. If it occurs later, close to the time of diagnosis, then it can only have got into the brain through rebel immune cells.

If Matthew's team is successful, this project will give the first real insight into why neurodegeneration occurs. This could make a huge impact on children with LCH and their families, as it could provide the foundations for future treatment strategies to prevent neurodegeneration.

Isobel Parmenter Memorial Fund

TEAM NIMMY
FUNDRAISING FOR LCH RESEARCH

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