Cognitive impairments in inherited metabolic diseases: Tracking outcomes across the life span

Dr Cristina Romani in collaboration with the Metabolic Team at Birmingham Children's Hospital

A new area of neuropsychological investigation involves cognitive impairments present in children and adults suffering from inherited metabolic disorders (IMD). Failures to synthesise different enzymes result in an accumulation of substances which are toxic for or interfere with normal cell functions and/or in a reduced ability to synthesise essential compounds. Examples of disorders involving accumulation of substances are lysosomal storage disorders (e.g., Niemann-Pick Type C, Fabry disease, Tay-Sachs, Gaucher's disease) and disorders of carbohydrate metabolism (e.g., galactosemia, Pompe disease); examples of disorders involving toxic effects of failures in amino acid and peptid metabolism are Phenylketonuria (failure to synthesize tyrosine) and Tyrosinemia (failure to degrade tyrosine).

Although the majority of these disorders affect a variety of different organs, neurological impairments are significant and prevalent in many of them. It is possible that neurons are especially affected because of their longevity and lack of renewal. Investigations of cognitive impairments in these disorders are only in their infancy because it is only recently that advances in our understanding of their biological causes, coupled with advances in dietary management and in enzyme replacement therapy have significantly prolonged the life and mental health of affected individuals. However, given these advances, it is now imperative that we reach a deeper understanding of the cognitive impairments present in these disorders. This is important for clinical managing of these disorders. Cognitive profiles need to be known for best integration of affected children and adults in educational and working settings. Cognitive profiles also need to be known to develop sensitive cognitive measures to monitor disease progression and assess the efficacy of different therapy options. In addition, these disorders can shed new light on the organisation and development of cognitive functions.

This project will test children with different metabolic diseases (but especially children with PKU and galactosemia) using an extensive battery of tasks to obtain a comprehensive picture of cognitive functions. Profiles will be compared across different ages and across different diseases. Cognitive scores will be related to one another (to see which clusters of tasks are impaired or spared together) but also to blood measures of metabolic control. Finally, cognitive and blood measures will be related to neuroimaging measures of brain functioning through stuctural MRI, resting state fMRI, spectroscopy and DTI analyses.

Results will have not only clinical implications, but also implications for our understanding of brain development. Different cognitive impairments in different diseases will offer us a special vantage point from which to investigate the neurological substrates underpinning different functions. In addition, within the same disorders there are sub-types which become symptomatic at different developmental stages (infancy, early childhood, late childhood/adolescence, adulthood). This will offer us the possibility to investigate how cognitive functions develop in sub-optimal conditions at different stages. Finally, there is evidence that cognitive performance is related to dietary/treatment compliancy. This will offer us the possibility to assess the impact of toxicity at different ages (e.g., exposure to toxicity during adolescence may have more impact on executive functions which develop at this time).