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THE INVESTIGATION AND SUB-CLASSIFICATION OF RENAL TRACT IMMATURITY IN CHILDHOOD ENURESIS USING NOVEL METABONOMIC TECHNOLOGY.

Aims of Study

Metabonomics[1,2] is an exciting and innovative technique, that determines systemic biochemical profiles and function regulation in whole organisms by analysing biofluids or tissues. The complex structure of the lower urinary tract, with co-ordination between several levels of the central nervous system required for functional control, means that enuresis has multiple aetiologies. Therefore, metabonomics, a non-specific and non-invasive analytical method is ideally suited to this complex problem. The aim of this study was to apply Nuclear Magnetic Resonance Spectroscopy (NMR) and Pattern Recognition (PR) technology (ie.metabonomics) to the differential diagnosis of childhood enuresis with the long-term goal being to avoid invasive urodynamics tests in these children.

Methods

Random urine samples were obtained from 53 children (age 1 month-16 years), with no structural or functional urinary tract pathology, which were designated a control group. Samples from 27 children (age 5-16 years) presenting with enuresis and no structural abnormalities or pharmacological treatment were also collected and designated the enuretic group. All children had a full clinical and laboratory history taken and their investigation results noted. 600 MHz ^{1}H NMR measurements were obtained on all samples and the metabolic profiles produced analysed using the unsupervised PR methods of hierarchical cluster analysis (HCA) and principle components analysis (PCA)[1,2].

Results

Analysis of the NMR data from the control group using HCA identified natural age-related groupings, namely 0-3 years, 4-7 years, 8-11 years and 12-16 years based on similarities in the urine biochemistry. PCA analysis of the same data showed an age related metabolic tragectory[3] within the urine biochemistry, as evident in PC1 and PC2 (33% of the metabonome). PCA analysis of both the normal and enuretic children's samples together revealed that 10 of the 27 enuretic children (37%) had urine that "clustered" with normal infants aged 0-3 years. This metabolic immaturity with respect to urine was also seen in two further enuretic children, aged 10 and 12 years respectively, who clustered in the 4-7 year area of the metabolic trajectory. Examination of the urodynamics performed on the 10 enuretic children showing metabolic immaturity showed some sub-classification. 5 of the children, aged 10-14 years, had features of hypertonicity and reduced bladder capacity on urodynamics in association with severe urinary metabolic immaturity. This group contained the children with refractory symptoms who were expected to have life-long continence problems. 4 children, age 5-8 years, had some unstable contractions but normal capacity and compliance, similar to those seen in normal infants on urodynamics, with mild metabolic immaturity. One child's urodynamics were not available

Conclusions

Metabonomics is a powerful non-invasive and non-selective approach to identify metabolic changes with age and urinary tract function through urine analysis. Using metabonomics, we have demonstrated for the first time, that renal tract immaturity, as evident in urine biochemistry is present in enuretic children. We hypothesize that the younger enuretic children with mild immaturity on metabonomics and urodynamics will 'catch up' with the normal children over time and gain continence. In the long term, metabonomics could be used to sequentially plot the urine biochemistry over time to show this and reassure children and their families. The metabonomic identification of those urinary constituents that separate enuretic children with sever metabolic immaturity from normal children controls could

ultimately lead to the development of new urinary diagnostic tests or form the foundation of new treatments.

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