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| **Mitochondrial respiratory chain disease and sudden unexplained death in infancy (SUDI) and Childhood (SUDC)** |
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| **Introduction** Disorders of mitochondrial respiratory chain (MRC) function represent one of the commonest inherited metabolic diseases. These may present at any age, with any mode of inheritance and with a wide clinical spectrum of disease manifesting as dysfunction of almost any organ or combination of organs. There are estimated to be over 1,000 genes involved in the expression of a functional respiratory chain. Diagnosis of these disorders is particularly problematic as measurement of respiratory chain function can only be reliably assessed in fresh tissues.  As a consequence, it is difficult to investigate MRC function in post mortem tissue and there is little published data on the possible contribution of MRC disease to SUDI.  Our hospital protocol for the investigation of SUDI includes: fat staining of frozen liver, kidney, heart and muscle, acylcarnitine analysis in dried blood spots and fatty acid oxidation flux in post mortem cultured fibroblasts. Fatty acid oxidation flux is measured in cultured fibroblasts as a screening tool to detect primary inherited defects of mitochondrial ß-oxidation. However, secondary reduction of fatty acid oxidation flux in cultured fibroblasts serves as a marker for altered oxidative metabolism/altered redox state within the cell and may serve as a surrogate marker for mitochondrial respiratory chain disease. The aim of our study was to analyse those cases of SUDI or SUDC that demonstrated reduced fatty oxidation flux.  **Material and Methods** Fatty oxidation flux was assayed in cultured fibroblasts by measuring the release as 3H20 from the labelled substrates [9,10-3H]myristate, [9,10-3H]palmitate and [9,10-3H]oleate.1-3  Results were reported as nmol per mg fibroblast protein per hour and expressed as a percentage of the mean of simultaneous paediatric control fibroblasts. Fatty acid oxidation flux was measured in each patient cell line in 2-6 separate assays using the 3 different substrates in duplicate. Mitochondrial DNA (mtDNA) depletion studies were by Pico Green staining and assessment of redox state was by Mitotracker/Tetramethylrhodamine methyl ester (TMRM).4 Fibroblast complexes were measured by spectrophotometic methods. 5  **Results** Over the past 20 years we have investigated >1800 cases of SUDI. After excluding cases with a primary fatty acid oxidation disorder, 27 remaining cases (1.5%) showed an abnormal fatty acid oxidation flux, strongly suggestive of an underlying respiratory chain disorder. Nine of these cases underwent post mortem examination at our institution. Seven of the nine cases were male and aged between 8 days and 20 months. In 6 cases the final cause of death was sudden infant death/ sudden death in childhood, SUDI or unascertained. In 1 case there was a cerebellar haemorrhage, in another a pulmonary haemorrhage and in another patchy bronchopneumonia of the left lower lung. In all cases the fatty oxidation flux was reduced, with low complexes in fibroblasts (3) and in muscle (1). In 3 cases there was mosaic mtDNA depletion in fibroblasts and a single *POLG* mutation of uncertain significance in one of these. Complex II was reduced in 2 cases and complex IV in another 2 cases.  **Conclusions** Our results demonstrate that a small percentage of babies dying suddenly and/or unexpectedly have low fibroblast fatty oxidation flux suggesting an underlying mitochondrial respiratory chain disorder. Further studies, where possible, by measuring respiratory chain complexes/Pico Green staining /molecular analysis provided some further evidence to support an underlying respiratory chain disorder.  There is need for further systematic research in this area to determine the nature of the association between respiratory chain disorders and the incidence of SUDI/SIDS. Improving methodology including ATP synthesis assays and more advanced molecular technology should facilitate progress in this area. |