Ceroid-lipofuscinosis (Batten Disease)

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Abstract

The ceroid-lipofuscinoses are a group of inherited neurodegenerative diseases occurring in human beings and animals. Histologically there is generalised accumulation of a fluorescent lipopigment within the cytoplasm of many cell types and selective necrosis of some populations of neurons. Clinical signs include loss of vision, seizures and mental retardation with premature death being the eventual outcome. Systematic analyses of isolated storage material have previously resulted in the identification of subunit c of mitochondrial ATP synthase as being a major constituent in the late infantile human, ovine, bovine and three canine forms of ceroid-lipofuscinosis. Saposins A and D have been identified as being stored in the infantile human disease.

Brain biopsy has been routinely used to diagnose ceroid-lipofuscinosis in sheep. The efficacy of this technique was investigated and it was concluded that it was a safe and reliable method for diagnosis in lambs aged $2\,^{1}/_{2}$ months. In contrast, diagnosis of the disease by clinical examination could only be made comparatively late in the disease course at 9-12 months. Repeated neurological examinations enabled "clinical staging" of the progression of the disease.

Haematopoietic cell transplantation was carried out in foetal lambs with ceroid-lipofuscinosis. Stable engraftment of an average of 9% blood cells was achieved but under the conditions of the experiment there was no alteration in the disease course or severity of lesions in transplanted lambs with ceroid-lipofuscinosis as compared to affected lambs without transplanted cells.

The observation of autofluorescence from storage cytosomes in the ceroid-lipofuscinoses has lead to the assumption that they contain a fluorophore of critical significance to expla nations of pathogenenesis. Studies on the nature of the fluorescence from storage bodies and isolated storage body components allowed the conclusion that no single significant fluorophore other than protein was present.

Antibodies to subunit c of mitochondrial ATP synthase were produced. These and similar antibodies from other sources were used for immunocytochemistry. The staining pattern observed varied, depending on the fixation regime, the antibody used and the form of disease. It was concluded that different epitopes were exposed in different forms of the ceroid-lipofuscinoses. Positive immunostaining of storage material in muscle and cartilage from the ear depended on the age of the patient and could assist but not replace current methods of diagnosis. Storage cytosomes were also labelled using immunogold staining at the ultrastructural level.

The ceroid-lipofuscinoses are a genetically diverse group of diseases which appear to have complex biochemical systems underlying them. The hypothesis was developed that the defect may lie in the disassembly of the F_o complex rather than in proteolysis *per se*. The aggregation of subunit c with lipids could result in a complex structure resistant to catabolism by proteases.

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