DOWN'S SYNDROME
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Down's Syndrome and Cytoskeletal Abnormalities

Despite the prevalence of Down's syndrome (DS), 1.5 per 1,000 births [23] and high societal costs involved, the basic biologic cause of the mental deficiency seen in this condition is poorly understood [6]. It is only through an understanding of the basic cause of intellectual impairment in Down's syndrome that potential therapeutic interventions might be developed.

The published literature suggests that in Down's syndrome the neuronal cytoskeleton may be abnormal. A mechanism by which the triplicated chromosomal material in Down's syndrome might cause cytoskeletal abnormalities will be discussed. Should these hypotheses be correct, then pharmacologic manipulations normalizing cytoskeletal expression in Down's syndrome might be possible.

Cytoskeletal components in neurons are composed of three families of polymeric proteins: intermediate filaments (as neurofilaments), microtubles and microfilaments. These structural proteins are involved in elaboration and maintenance of axonal and dendritic ramifications, movement of intracellular molecules and organelles, and at the synaptic level may be involved in the process of learning [11,16,18]. Any abnormality of cytoskeletal components might lead to widespread neuronal malfunction and clinically to mental impairment.

Abnormalities in cytoskeletal expression may be common to a number of conditions associated with mental deficiency. For example, in hypothyroid experimental animals microtubule assembly is defective [10], there is a reduced number of microtubular profiles seen with electron microscopy [9], and neurofilament-antigen expression is delayed in selected axonal systems [26]. In phenylketonuria, a disorder of phenylalanine metabolism, there is an 8-fold increase in the concentration of phenylalanine at the carboxyl terminal of tubulin, a component of microtubules, suggesting that neuronal impairment may be on the basis of defective microtubules [33]. Also, in an electron microscopic study of cerebral cortical tissue taken from individuals with mental impairment microtubular disarray was noted [3,31].

In Down's syndrome, cerebral cortical tissue, when stained with Golgi techniques, has revealed abnormalities in dendritic arborization and in dendritic spine shape and distribution [21, 22, 38, 39]. Dendritic atrophy has also been noted in Down's syndrome cortical neurons during postnatal development [1]. These morphologic results suggest that there may be an abnomal underlying cytoskeleton. Quantitative neuropathologic studies have shown a decreased number of cortical neurons [34,41]. These results suggest slowed neurogenesis which maybe on the basis of defective cytoskeletal interactions during neuronal mitosis and migration.

Possibly the strongest line of evidence implicating cytoskeletal abnormalities in Down's syndrome is the universal appearance of the neuropathologic findings of Alzheimer's disease in elderly Down's syndrome individuals [20, 40]. Alzheimer's disease is typified by the accumulation of abnormal fibrillary material which shares antigenic determinants with neurofilaments and microtubules [11, 30]. It is tempting to speculate that in Down's syndrome the neuronal cytoskeleton might be regulated in a fashion different from normal, thus predisposing to the eventual development of Alzheimer's disease.

To investigate the possibility that neuronal cytoskeletal components might be regulated in a fashion different from normal, the author applied a monoclonal antibody (mab N210), which recognizes the 210 Kdalton neurofilament subunit [17], to autopsy-derived, formalin-fixed Down's syndrome and normal brain tissue sections. The specimens were obtained from individuals who died during the first few months of life. The results suggested precocious neurofilament antigen expression in Down's syndrome, early in life [27]. Also mab N210-staining profiles within axons seemed to have a larger caliber in Down's syndrome as compared to normals. These results suggested that indeed there is a difference in neurofilament antigen expression in Down's syndrome as compared to normals.

Microtubule assembly has been shown to be abnormal in brain tissue taken shortly after death from patients with Alzheimer's disease [15]. The neurofilament antigen expression results in Down's syndrome suggest a similar implication: aberrant regulation of normal cytoskeletal components may be predisposing factor in the development of Alzheimer's disease.

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Michael Grimaldi, exploring with joy, age one year (trisomy 21)